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THE CHANGING ORDER IN MEDICINE *

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I WOULD be very neglectful of my opportunity and very untrue to my deep feelings if I failed upon this occasion to record my great appreciation of the progress the American College of Physicians has made and is making in the rôle of leadership in the field of internal medicine, and also my very deep and heartfelt appreciation of the privilege and honor which has been conferred upon me in my selection to preside over the activities of the College during the past year.

College Matters. This year has been fruitful in accomplishments. The affairs of the College have continued to prosper, and this is due in no small measure to the faithful devotion of the Board of Regents and Governors and particularly to the extraordinary faithfulness and ability of our executive staff under the leadership of Mr. Loveland.

Our main function, that of postgraduate education, was notably furthered at our Philadelphia meeting, and this meeting which we are holding in Detroit is also a notable landmark in our progress. We have met here under a cloud of sorrow caused by the sudden death of our beloved associate Dr. Charles G. Jennings who, before his untimely end, had already organized the clinical program which we have been enjoying, and whose devotion to the highest ideals of the College has been notable during many years of service upon our Board of Regents. His loss is irreparable, but the memory of his life will always remain an inspiration to all of us who have been associated with him.

In connection with our educational activities we are all increasingly aware of the important part which our journal, the Annals of Internal Medicine, continues to play in this field. The Annals has continued to grow both from the standpoint of the high character of the scientific contributions to medical literature which it presents, and also in the support from subscribers and advertisers which is founded upon a growing appreciation of its value. We owe this in no small part to the able and skillful leadership of its editor.

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The general financial condition of the College is extremely satisfactory and has been ably directed by our Finance Committee and our treasurer.

There are two developments in the affairs of the College which have occurred during the past year, to which it seems timely to call special attention. The first of these is the serious consideration upon the part of our Officers and Regents of the desirability and possibility of acquiring a permanent home for our College. There are many reasons why this seems desirable, and if feasible it will add dignity and assurance of permanency to our organization. That this plan can be even considered is due fundamentally to the soundness of our financial position, and it is not unlikely that in the near future the ownership of our own home may be an assured fact.

The second notable development is the direct outcome of a policy strongly urged by my predecessor in the office of President of the College, Dr. Jonathan C. Meakins. I refer to the leading part which we have taken in the formation of a National Board for the qualification of internists.

A number of the Board of Regents, under the leadership of Dr. Meakins, for several years have been impressed with the need of better standardization for qualifications leading to the designation of experts in the field of internal medicine, and have felt that our College should take the initiative in meeting the problems raised by this need. Consequently, by vote of the Board of Regents and with the approval of the proper authorities of the American Medical Association, a joint Board of Medical Examiners has been organized for this purpose, under the combined auspices of our College and the Section on Medicine of the American Medical Association. This Board is expected to function effectively in the near future, and by establishing suitable criteria for the qualifications necessary for the designation of specialists in the field of internal medicine will do much to raise the standards of our practice, to develop a more adequate recognition of the special field of medicine, and incidentally will, we believe, do much to improve the standards of qualification for membership in the College of Physicians. We are all very much indebted to the very efficient and arduous labors of the special joint Committee which has been struggling with the many ramifications of this plan during the past year under the chairmanship of Dr. Walter L. Bierring.

More General Problems. While of course we have met here on this occasion under the auspices of and directly in the interest of the American College of Physicians, I am not unmindful of the fact that we of the College are merely one representative part of that larger and more important group, namely, the physicians of America. Consequently, I propose upon this occasion to address you upon some of the problems in modern medicine which seem to me to be of importance to the medical profession as a whole, and in the solution of which we of the College ought to play an active rôle.

It is, of course, obvious to all of us that we are living in a period of change, difficult but extremely interesting and affecting all the relationships of our social order, including that of the practice of medicine.

In the midst of the troubled and even anxious thoughts which the unrest about us may create there is some comfort in the recollection that this is not the first period in history in which civilization as a whole and medicine in particular have gone through similar experiences of change, sometimes approaching revolution but always leading eventually to progress. The period in the world's history when civilization as a whole and medicine as a part of that civilization remained stagnant, nearly dead, was that long thousand years known as the Middle Ages. There was no thought of change during that period, no stimulus of new or revolutionary thought, and in medicine the dogmatic dictums of Galen reigned supreme and unchallenged, and medical thought was like a flickering candle barely kept alight in the recesses of the monasteries. The sixteenth century and the Renaissance brought changes, rapid and frequently revolutionary, in all fields of social endeavor, and medicine shared in this reawakening, largely under the influence of more exact knowledge founded on the study of pathological material through autopsy. But in the light of our modern knowledge even this progress was very halting and imperfect. It was not until the early part of the nineteenth century, following the French Revolution and the Napoleonic era, that very great and important contributions to the knowledge of disease were made under the influence of such leaders as Bayle, Laënnec and Louis in France, and in the field of pathology particularly by Virchow in Germany. But the really revolutionary period came in the latter part of that century, with the development of our knowledge of the rôle of bacterial infection in many diseases, with the names of Pasteur and Koch standing out preëminently as leaders in this new field. It is since those days of 1870 to 1880 that the greater part of the fabric of modern medicine has been created, founded upon the increasing knowledge gathered by unceasing laboratory and clinical research, in such astonishing fashion as to be really bewildering albeit inspiring to those of us who have been privileged to live during this epoch.

But our intense interest in all of these developments has required a devotion of time and concentration of effort, which has quite naturally tended to make our profession individualistic in its approach toward medical problems and often oblivious to other important elements in our social fabric because of the very fascination as well as absorbing interest of the new knowledge which has so rapidly and constantly been developed in our own chosen field.

It is not to be wondered at, therefore, that in our habits of mind as well as in our practice we have tended to become individualists.

But during these latter years the practical application of our growing medical knowledge has become increasingly evident to the world at large, and the same principles which guide us in the treatment of our individual patients are recognized to have great significance to the community as a whole. So that one of the most important changes that have occurred is the realization that society as a whole is interested in these problems quite

as much as is the physician, and that the practical solution of them is perhaps even more the concern of the community than of the physician himself. No longer, therefore, is the physician a man apart, a sort of high-priest of mystery giving out his solemn pronouncements dogmatically, unconcerned with explanation of the reasons why; but rather an enlightened and interested public expects and demands a reasonable understanding of what is going on, and also an extension of our activities far beyond the intimate personal relationships between the individual patient and his physician, to those broader fields which we designate as preventive and social medicine.

Thus, the physician, whether he will or no, has been brought out of his cloistered existence into the field of active participation in community movements of great significance, in which he must play a part as leader, educator and guide or else stand adjudged unworthy at the bar of an exacting public opinion.

This changed relationship has brought us face to face with many problems which previous generations have not considered medical at all but which are pressing upon us for solution. It is of some of these that I will briefly speak to you on this occasion.

Changes Due to the Increase of Medical Knowledge. Before, however, we consider these outside relationships it is apparent that many changes in medical practice are due to the rapid development of our knowledge in many directions. Some of these may be briefly summarized.

One of these, of great significance, has been emphasized in Professor Cannon's address to us this evening, that is, the development of the physiological approach to many problems, as distinct from the strictly pathological approach which has been the main basis of medical science up to recent years. It appears to be evident that a closer study and appreciation of functional disturbances during life are to take a much larger share in our medical thinking in many fields. This field of study is difficult, and in it we have only made a beginning, but it offers opportunities for further progress which may have great importance and significance.

Then, we note the great progress in our knowledge of chemistry as applied to biology and to medicine. Processes which we have been accustomed to consider as morphological, now appear to have their ultimate basis in microscopic chemistry. Not only in the diseases of metabolism but also in the infectious diseases, where the chemical constituents of pathogenic bacteria together with the character of the tissue reactions which they cause are now being studied, chemistry is becoming increasingly important.

Of course, in the field of the hormones and the vitamins we have seen a rapid development of our knowledge, due to chemical research.

In general, our conceptions of the physical structure of living matter, the chemical changes which accompany vital activities, and our increasing knowledge of chemical substances which may control such activities, are the result of modern research. These researches have also led to a marked advance in the development of pharmaceutical preparations and to definite improvement of numerous therapeutic agents placed at our disposal.

Then we have the fascinating new field of knowledge opened up by the discovery that ultramicroscopic viruses are the causes of some of the important infectious diseases the etiology of which has heretofore baffled us during the bacteriological era. These researches open up new fields of knowledge and give promise of better control and treatment of these diseases.

One of our great problems is to keep abreast of all this new knowledge, so that we and our patients may receive the maximum benefit from it. We must continue to be students as well as practitioners, and there is always real danger that our practice may lag behind the advance of medical knowledge.

Changes Due to the Application of the New Knowledge. It is here that we move out from our narrower, strictly professional sphere into our contacts with the community.

Specialism. One of the first of these changes has been due to the very amount of new knowledge which has made it impracticable, even impossible, for any one mind to grasp all of the ramifications of this new knowledge and to make the best use of it.

It is this fact, I think, rather than any economic motives, that has led to the development of specialism in medicine.

No one who has grown up in the medical profession can fail to have the highest respect and the deepest affection for those representatives of our profession who have carried on against the greatest difficulties with courage and devotion and who have been not only the physician but also the wise counselor and friend of the families entrusted to their care. All honor always to the general practitioner!

It is obvious, however, to them as well as to the rest of us, that if the highest attainment of skill and knowledge is to be at the disposal of the community, many of us must devote our special attention to certain specific lines of study and of practice. In losing some of the personal touch of the family physician there has nevertheless been great gain in the development of better diagnosis and treatment. How to hold the advantages of each of these groups and to have them go on together to their mutual advantages and particularly to the advantage of our patients, is one of our modern problems.

I feel that we are taking an important step forward toward the solution of this problem in the plans which have been formulated for the application of standards by which specialists in internal medicine may be recognized, and it is particularly to be noted that in this plan special emphasis is placed upon the essential importance of an adequate preliminary training in general medicine, as the foundation of any specialty.

The defects in the practice of the specialties would appear to revolve mainly around the temptations to their abuse through false or misleading claims of special proficiency, through the multiplication of unessential and costly procedures, or through inequitable professional charges, in a word they are due to the commercialization of the public demand for expert serv-

ice. Surely, we as a profession should be able to control and to remedy these evils.

Preventive Medicine. Perhaps the greatest change which our new knowledge has brought to us is the widening of our sphere of responsibility from the care of the individual patient to that of the community of which this patient is a part. This is particularly true, of course, in the field of infectious diseases where the protection of others is quite as important as the cure of the individual patient. There are, however, applications of this principle other than that of preventing the spread of infection.

Thus we have the developing field of responsibility for large groups of individuals who are not apparently ill. Great progress has been made in the survey of such groups through the operation of medical services for industry, for life insurance and for schools, and also through the movement to educate individuals to the importance and advantage of periodic health examinations at the hands of their own physicians.

The results of such surveys have already uncovered a large number of unsuspected cases of disease in incipient and remedial stages. But this progress has largely been due to the operation of organized groups associated either with governmental or with industrial agencies. The individual practising physician has taken too little share in this movement, due largely to faulty training which centers our interest upon obvious disease and has failed to develop a technic and interest in the recognition of slight deviations from the normal which have not yet led to symptoms or complaints on the part of the patient. Not only has the bulk of the population not been educated to the point where the average man would consult a physician for a regular check-up once or twice a year, just as he would his dentist, but also the few who do often have their enthusiasm dampened by the lack of interested response on the part of the physicians whom they may consult. This whole field demands a different outlook both in our medical education and in our medical practice.

Then we have the whole field of prophylactic and preventive inoculations, best exemplified by their use in smallpox and diphtheria but also applicable to other diseases. There is also the large field of remedial physical defects found especially in childhood, such as defective teeth, tonsils, adenoids, eyesight, faulty nutrition and the like. These conditions in themselves do not constitute disease but are the underlying and predisposing causes of many diseases.

We have left this field of service very largely to our public-health and school authorities, excepting in so far as the pediatricians take part in it. As a group the pediatricians may be fairly characterized as the best exponents in our profession today of the highest type of general practice combined with an appreciation of the responsibility for preventive medicine. But we should not leave this field entirely to our public-health authorities and to our pediatricians.

Very recently a new potential force of great significance has been added

to the public-health movement. I refer to the provisions of the Federal Economic Security Act which will make available nearly twenty million dollars a year to be expended through the Public Health Service and the Children's Bureau.

Serious problems are here involved. In what directions are these funds to be expended, how will their administration be affected by political considerations, what properly trained personnel is available, and how will these new activities be related to those of the medical profession?

These great appropriations signify enormous possibilities for improving the health of the nation, but they also constitute a new opportunity and a challenge to the medical profession.

In the first place, in these days of professional insecurity an attractive field of service is opened up to many physicians. I must confess that were I at the present time in the stage of my medical career which I was passing through when five or ten years out of the hospital, this prospect for public-health service would have a great appeal to me. I hope that there will be many of our younger best trained physicians who may become enlisted in this public-health service.

In the second place, however, we must realize that this new development will greatly strengthen the organization of our health authorities and might easily lead to an increase of the amount of public or state medicine. Dr. Thomas Parran, Jr., the Commissioner of Health of the State of New York, who undoubtedly will have a considerable influence in the formation of these new policies, hopes that it will "liberalize present medical practice, coördinating it with public-health and medical services." He would propose "to assist the private physician by providing for him laboratory, hospital, nursing and other facilities for the treatment of his cases, and at the same time relieve part of the load of catastrophic illness from the low-income group."

In this or some similar manner we as physicians must coöperate in this movement or face the possibility of the slow advance of State medicine.

What a wonderful power we, as a body, could exert in this field if we each individually constituted ourselves health officers for the families under our care, detecting and correcting defects, following up sources of infection in syphilis, in diphtheria and other infectious diseases, checking the contacts in our cases of tuberculosis, and in general in every way coöperating closely with our health officials in their efforts to prevent disease! This is the challenge of preventive medicine to us. We must either take our proper place in this field or we will surely be pushed aside.

Mental and Emotional Problems. There is another field perhaps even less well understood and possibly more important than those we have been considering. I refer to those influences of our modern life which affect the behavior and the mental, nervous and ethical reactions of individuals.

There can be no doubt that the tremendous incidence of various forms of insanity, of mental deficiency as well as of functional nervous disorders

is susceptible of decrease by preventive measures, and for the prevention of these conditions the medical profession must take considerable responsibility.

The rôle of syphilis in the causation of many forms of mental and nervous disease is known. But even here we are doing comparatively little to apply well established principles of treatment. When we come to other disorders of which the causes are less definite, as for example, faulty inheritance, faults of early childhood environment or education, or the pressure of modern social, business and industrial life, how little are we, as advisers, doing to influence either the environment in which we all live or the individual habits of the patients under our care!

Perhaps the lack of intimate personal contact which we have lost in the passing of the family physician is a factor in the situation. But whatever may be the explanation, is it not true that we, as physicians, under the influence of our passion for modern and exact science have lost sight of those more intangible and less demonstrable factors which we call the nervous and the psychic? Not only in the prevention of actual nervous or mental disorders is this factor important but also in the treatment of our patients suffering from any disease, particularly the chronic disorders. A better recognition of the importance of their mental processes would appear to be demanded which would bring us back to a fundamental appreciation of our patients as individuals rather than as cases of disease, and to an understanding of their personalities and the influences under which those personalities have developed and are manifested. Is it not at least partly true that the extraordinary development of cults of faith and mental healing in this country, estimated to affect approximately ten millions of our people directly or indirectly, may be attributed to a lack of interest in and appreciation of these factors by the practising medical profession? Personally I have a very strong feeling that as a whole we of the profession are constantly losing magnificent opportunities not only to help our patients get well but also to control and develop their characters and personalities as evidenced by their nervous and emotional as well as their intellectual responses. In other words, have we not been affected too much by materialistic and scientific progress and failed too often to appreciate the importance of the individual as a whole, which would include all of these psychic, emotional and ethical values in his life as well as the physical?

Biological Aspects. Our consideration of certain aspects of preventive medicine has emphasized particularly the prevention of disease and the saving of human life. As far as the general population is concerned this means that we have been attempting to diminish subtractions only. But what about the additions? I refer to the control of increase of population. Have we physicians any responsibility for this?

This is perhaps a somewhat new slant on community responsibility to most of us. The problem, however, is with us. In certain centers the pressure of overcrowding and overpopulation is acute, and in times of economic depression the effect not only upon comfort and happiness but

also upon health and life itself is very real. Students of biology are becoming very much interested in this problem. It is, of course, a part of the general field of eugenics which is concerned not only with the quantity but also with the quality of the population.

At the present time, where this problem concretely confronts the physician is in the question of limitation of births, as involved in contraception and in the interruption of pregnancy. It is not my purpose to deal exhaustively with this highly disputatious subject. But I simply wish to lay before each of you some thoughts for your individual consideration.

Many of us certainly cannot accept the doctrine which sacrifices the threatened life of the mother for the potential existence of the infant. But I wish to raise in your minds the searching individual question whether our modern tendency to exercise our opportunities for advice concerning contraception and the interruption of pregnancy has not been gradually and increasingly influenced by personal and economic considerations, whether, in other words, we are not becoming gradually calloused to a lack of appreciation of the value of human life as such, and whether, particularly in our large cities under the pressure of economic conditions, we are not imperceptibly laying ourselves open to the criticism from certain religious quarters that we are unjustifiably and unethically interfering with natural processes?

I further wish to raise the question in your minds as to whether our approval of contraception in general has not imperceptibly led to a change in our attitude toward the ethics of the other problem, that of early abortion, and as to whether this, if true, is not having its influence upon our conception of the sanctity of human life in itself and consequently upon our attitude toward family life in general as the basis of our society? In other words, are not some of our critics at least somewhat in the right in suggesting that tendencies in this direction might lead us ultimately in the direction already followed in Soviet Russia?

Another aspect of this same problem is raised by the recent discussion concerning the ethics of euthanasia. I think that there is little doubt that we are all pretty much in agreement on this subject, but I again raise the question as to whether the support of euthanasia in some quarters and the interest which the public discussion of it has aroused are not again indications that there is an imperceptibly changing point of view toward the sanctity of human life?

Social and Economic Problems of Organized Medicine. Perhaps the greatest recent changes of all in our medical relations have been those which involve the social and economic order. According to the recent trend these relationships also involve important political ramifications, so that we find ourselves as a profession brought face to face with many problems which have not particularly concerned our forefathers in medicine. Important questions of serious moment have been raised, and we cannot escape some consideration of them, much as we might prefer to devote our time and energies to more strictly medical problems.

The recent widespread interest in these problems was probably crystallized about the reports of the Committee on the Costs of Medical Care. After several years of very extensive study this Committee brought out reports which, while they contained many data of interest and value, led to a division of interpretation among the members of the Committee itself and have precipitated a widespread and sometimes acrimonious discussion among the medical profession and the community at large.

I think that any fair-minded person who has studied these reports will appreciate that they reveal conditions heretofore incompletely recognized and understood, which demand serious consideration and, if possible, remedy. The most important of these perhaps are those which relate to the unequal distribution of the burden of sickness, the unequal and often inadequate compensation to physicians, the unequal and inadequate provision of medical services in many communities, and the disproportionate cost of notoriously ineffective instruments of treatment such as proprietary and patent medicines as compared with the cost of adequate medical and hospital service.

All of us who practice medicine are well aware that long illness is a great burden, often a crushing one, upon our patients, and we have long been accustomed to adjust our own services and their cost to existing circumstances. All fair laymen recognize the fact that, as a profession, our aim and ideal has been the provision of services rather than insistence upon adequate financial compensation. That there are exceptions to this rule also, we of course all well know. But in our hearts we are assured that we cannot in fairness allow the motives of our profession as a whole to be impeached.

The consciousness of this fact should not lead us, however, to contend that because in general we know that our motives have been generous and fair, consequently all is well and no changes are desirable or necessary. It is very probably true that with the improvement in general social conditions in the United States there has also been an accompanying improvement in the character of medical service, and very likely, as has been claimed, no country in the world enjoys better medical service than ours.

But this is far from sufficient. The very progress that we have made is an incentive and challenge to further improvement, and it would appear from recent studies and analyses of the situation as it affects medical practice in this country that the need for such improvement does exist, and we are all individually conscious of that fact. Consequently it would appear to be a great mistake for us as a profession, either individually or as an organized body, to resist as unnecessary and unfair the demands for a study of this situation and for the application of appropriate remedies when and if they are found necessary. It is very gratifying to know that the recent trend in organized medicine is away from a general denial of such need and is turning toward a more rational study of the situation and a willingness to coöperate in making reasonable changes.

Quite properly, however, we as a profession insist that the problems of medical care are better understood by the medical profession than by other groups. Without in any way denying that the community as a whole, the members of which, when sick, constitute the patients under our care, is directly and primarily interested in these problems, nevertheless we feel that by our experience and training we are the ones best qualified to understand the various ramifications of this problem and to take the leadership in applying effective remedies. This can only be done, however, if, as individuals and as a body, we approach this problem with the same open mind and scientific spirit with which we would approach a more strictly medical problem.

Already considerable progress is being made in this direction. In the past few years a very large number of experimental activities looking toward a more equitable distribution of the cost of illness and remuneration of physicians have been instituted under medical auspices. The results of these experiments are varied and as yet inconclusive, but it is evident that progress is being made. It appears that quite independently of the financial and economic factors involved, our chief concern as physicians should be that high standards of professional service be maintained and that any proposed change should improve rather than impair these standards.

The immediate burning question, about which considerable discussion and debate have already occurred, is that of health insurance. This method of meeting the problem has been generally adopted in the countries of Europe. Studies of the operation of these systems have led to conflicting reports as to their results. But from the discussion, I think, has come a realization that there are many defects in existing health insurance systems and that, taken all in all, with the conditions as they exist in the United States the adoption of compulsory health insurance, as organized in England and Germany or even in Denmark where it has been most successful, would be an unwise experiment for this country. It is, therefore, I think, a matter on which we are to be congratulated that plans to include health insurance in the National Economic Security Bill were laid aside by the present Federal Administration. This result was due very largely to the arguments raised by members of our profession, and in so far as this change in the proposed plan was due to medical opposition, it places upon the organized profession an increased obligation to make every effort to solve the problems involved by other means which may give the good results sought by compulsory health insurance, without incurring the objections and dangers which it entails.

It is estimated that there are at least sixty types of experiments now going on in various communities of this country along these lines at the present time. Some of them are already obvious failures, others are apparently fairly successful. All of them appear to have some defects. Under a broad-minded leadership our profession should be in a position to analyze

and assess the value of these experiments. Such a study will take time and money as well as special ability. In view of the great service it might be to the cause of public health and general welfare in which the Foundations are interested I very much hope that they may join with organized medicine in a coöperative analysis of these important experiments. Such enlistment in a common cause might also serve to bring closer contact between the great health Foundations and the organized medical profession. In recent years there has been an unfortunate tendency for them to be arraigned in opposite camps. Now, it so happens that I know the leaders of these social groups very well. They are a fine lot, quite as fine in their way as we are in ours, and, I may add, they also have similar failings as well as similar virtues, in other words they, too, are human.

The interests of these Foundations and of the medical profession are in the long run the same, and they can only be best served if the representatives of each work shoulder to shoulder to solve these important problems, without any self-seeking motives and particularly without bitterness and jealousy. Evidence that this most desirable state of affairs is gradually coming about is now appearing, and I feel more confident than at any other time during the past few years that wise and equitable solution of this problem will eventually be evolved.

Medical Personnel. One phase of the problem, for which the medical profession is largely if not exclusively responsible, is the question of the amount and caliber of medical service which is available. As to quantity, this goes back to the number of physicians, and in these days when the path of least resistance leads the youth of our country to further study rather than an attempt to get a job, our medical schools are flooded with applications, the number of graduates in medicine has increased and the saturation point of numbers has already been reached in many of our communities.

Judging by the low average rate of income of physicians and the struggle of the younger members of the profession in our large cities, one suspects that either there are too many physicians or else that their distribution is faulty. That the latter is true in many communities of our country has been demonstrated. It would therefore appear to be our first responsibility to take the lead in supplying better distribution of service where needed, and then, on the other hand, to bring pressure to bear upon our medical schools to restrict the number of graduates to the need, while at the same time improving their quality, by which we mean higher standards of ethics and ideals quite as much as improved intellectual proficiency and professional training.

The representatives of our best medical schools are well aware of these problems and are giving serious thought to the responsibilities which devolve upon them. It is not too much to hope that they will be able to meet this phase of the situation adequately.

Hospital and Dispensary Abuse. Another burning question in our large

cities is what has been termed hospital and dispensary abuse, by which we mean that these institutions which owe their efficiency mainly to our voluntary and unremunerated medical service, are patronized by many who economically are in a position to pay for private medical service, thus putting the physicians in a position of serving in the hospitals and dispensaries against their own economic interests.

Quite properly the representatives of organized medicine are insisting that safeguards against this abuse be thrown about the hospitals and dispensaries, and progress is being made in this direction. They are, however, making other recommendations of more dubious propriety, in my opinion. I refer particularly to the suggestion that all physicians in hospitals and dispensaries should be paid for the medical services rendered. If this were done, we would in the first place put an overwhelming increased financial load upon the administrative expense of these institutions. In the second place we would be demanding as physicians compensation for services which it has always been our pride and boast that we have given freely. A great deal of the criticism of the medical profession of recent years has been counteracted by the appreciation of the high-minded, generous contribution of service to the sick poor which we have always made. It would appear to be a great pity to take away this privilege as well as strategic advantage from our profession. Moreover, all of us in this body appreciate the fact that our postgraduate education depends upon our hospital practice and that we are only too happy to do this work because of the opportunities for improving our medical competency and the joy that we have in the acquisition of new knowledge.

Another phase of the subject which we cannot afford to overlook is that the placing of all of the staff of our State and municipal hospitals upon a salary would tend to make these positions more political and create a real danger that in this very plan so strongly recommended in some medical quarters we would be taking the first step toward that anathema of organized medicine, namely, State medicine.

That there exist, however, many instances in which hospital or dispensary practice infringes on the rights and privileges of individual physicians, there appears to be little doubt. Changes in the existing order may be desirable, but we, as physicians, are interested both in the institutions and in the individuals, and we should make sure that any such changes are mutually fair and beneficial to both parties.

Socialized or State Medicine. This leads us finally to the consideration of socialized or State medicine as a present-day problem in medical economics.

In the first place, I think, we must recognize the fact that we already have a considerable amount of State medicine in this country, with the apparent approval of the medical profession. We see it in the State care of the insane, of the mentally defective and of the tuberculous, we see it in the Army and Navy medical service, we see it in many of the activities in the

field of preventive medicine under the control of the public departments of health, and I have already discussed the possibility of its extension under the Social Security Act.

During the depression we have also seen a very insidious extension of State supervision of medical service in the administration of medical care for those on home relief. In some communities this is very wisely and properly administered, with the coöperation of organized medicine through the county societies. But medical safeguards are often objectionable to administrative authorities, and there are not a few who are in favor of paying straight salaries for physicians engaged by the State for this medical service. Properly organized, controlled and supervised, this very need for home medical relief which our present economic distress has brought out can be utilized for the improvement of medical service from both the curative and the preventive aspects. In some communities this is being done, high standards of medical practice have been set up and insisted upon to the mutual advantage of the sick poor and of the physician. Where medical control of this service, however, is replaced by purely administrative or political control, the danger is great that medical standards will be lowered and the opportunities for progress not only lost, but actual deterioration of the present standards of service may result. This is of course exactly what we fear in what is called State medicine, and the fears are well-grounded.

Not only have we seen tendencies leading toward a mechanical and superficial character of medical service in medical home relief under State auspices but also in the operation of the workmen's compensation laws in many States we have had a very instructive illustration of the demoralization of standards which is always likely under a system of medical service under political control. Some of these workmen's compensation evils are being corrected in some communities, but only when active and wide-awake members of the medical profession have been alive to the situation and have taken an active part in remedying the abuses and eliminating faulty methods.

Not the least important responsibility of the medical profession in this field of economics is the insistence upon high ethical standards as distinct from merely high standards of medical proficiency. We are all of us aware of the insidious infiltration of our standards of professional probity which has been brought out under the stress of the economic depression. There has recently been published a sordid story of the practice of medicine at its worst. The author of this book evidently speaks from first-hand knowledge, and the allegations made are sufficiently plausible to bear the stamp of actual experience leading us through many sordid details into the haven of socialized State medicine as the remedy. This would appear to be an extraordinary deduction, but at the same time this line of argument probably represents the opinion of a considerable number of people both within and without our profession, and consequently cannot be entirely disregarded.

In the first place it is obvious that the experience of this physician was

very unfortunate and represents a very small fraction of the profession. One would like to know a little more of the professional company which the author kept before he became a convert to the doctrine of State medicine, and would particularly like to know whether there are no ways and means available of correcting these abuses by bringing those guilty of them out into the open on charges of unprofessional conduct. I am convinced that if we could simply expose these instances of unethical conduct they would quickly defeat themselves, but we as a profession have been perhaps too complacent in regard to them and too negligent of active efforts to eradicate them. On the other hand, if the undesirable elements of our profession are not eliminated, a system of State medicine would be apt to find these very individuals in control of such a system and much more powerful and dangerous than they are at present. We need to clean house of these elements and at the same time to control the situation at the source, namely, in a more rigid selection of those admitted to our medical schools and to medical practice.

Conclusions

I feel that we have wandered considerably afield in our discussion of the changing order in medicine.

The main thought which I have wished to emphasize is that there exists a pressing necessity for the medical profession to adapt itself to modern changing conditions.

We ourselves are mainly responsible for putting our house in order, and if it is in order we need have no fear that it will be sold over our heads either to irregular cults, to socialism, to the State, or to anyone else.

Our chief objective must always be to develop the art and science of medicine. But without sacrificing this main objective we must widen our interests to include those of the community as a whole. As we move out of our cloistered life of concentrated interest in our own special and fascinating job into the larger field of more general human interests we have the opportunity for a greater service which will be less individualistic and more social-minded. Thus will our horizon be immeasurably widened and we ourselves may at the same time become better physicians and better citizens.

God forbid that we should wrap ourselves about in the cloak of self satisfaction, content with our own immediate objectives and past achievements, or that, on the other hand, we should assume an attitude of aggressive trade unionism, intolerant of criticism, resistant to change and insistent upon our own special privileges and interests to the exclusion of those of others!

As individuals and as a profession we need to take thought of these matters and then move on to meet the challenge in a manner worthy of the fundamental principles and the high ideals upon which our profession is founded.

Without presuming to present any specific program of action, the prin-

ciples upon which such action should be based might be formulated as follows:

1. A strict adherence to Truth both as we now know it and as it may be developed in the future by continued persistent research into the as yet hidden secrets of Nature.

2. An absolute ethical Honesty. Honesty in our thinking as well as in our professional conduct.

3. A devotion to the spirit of Service. Service not merely to those individuals entrusted to our care but to the whole community.

May we ever be able truthfully to claim for our profession that our inspiration is the opportunity for service, not the hope of reward!

LYMPHOPOIESIS, LYMPHATIC HYPERPLASIA, AND LYMPHEMIA: FUNDAMENTAL OBSERVATIONS CONCERNING THE PATHOLOGIC PHYSIOLOGY AND INTERRELATIONSHIPS OF LYMPHATIC LEUKEMIA, LEUKOSARCOMA AND LYMPHOSARCOMA *

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It is doubtful whether there is any group of diseases about which there is more controversy over the clinical classification, pathogenesis and morbid physiology, than those which primarily involve the lymphatic tissues. As contrasted with those dyscrasias which have their origin in the sister blood forming tissue, the bone marrow, the greater difficulty in the interpretation of morbid processes in the lymphadenopathies is quite manifest. Thus, while the division of the diseases affecting the bone marrow into various categories is unanimously agreed upon and the principal features of their pathologic-physiology are accepted with little dissension, the mechanism and meaning of pathologic alteration in the lymphatic tissues remain today almost as obscure and chaotic as for the past fifty years. Witness, for example, the popular use of the terms lymphoblastoma and lymphoma, designed to encompass most of the non-infectious lymphadenopathies. The continuance of the use of such vague general terms is an admission of the confusion that prevails in this field.

The reasons for the difficulties that have continued to beset workers in this field are not difficult to find. They are largely, if not entirely, the obstacles that attend the interpretation of the histogenesis of the lymphocyte. No completely satisfactory concept of the identity, life history, and specific functional potentialities of the lymphocyte has yet been accepted. The fundamental cytological studies of Sabin and her associates have gone farthest perhaps toward establishing this cell in its proper relationship to the other cells of the blood forming tissues,[1] and are basic to any interpretation of the rôle of this cell in the lymphatic dyscrasias.

* Read in part May 1, 1935 at the 19th Annual Meeting of the American College of Physicians, Philadelphia, Pa., under the title "The Fundamental Mechanism in the Production of Chronic Lymphatic Leukemia."

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The problem of chronic lymphatic leukemia is essentially the problem of the pathologic-physiology of lymphopoiesis. Any rational attempt to trace the course of events in which the lymphocyte plays the dominant rôle must take into consideration the well established facts relating to the known pathologic alterations in which this cell type is the chief reacting unit, and also must be consistent with the physiologic conditions under which this cell reproduces itself. Further, it is clear that the unsatisfactory state of our understanding of both the physiology and the pathology of lymphopoiesis directly reflects the uncertainty and conflicting opinions that prevail with regard to the lymphemic states. Admitting, then, that any discussion concerning the mechanism of chronic lymphatic leukemia is hampered by our incomplete knowledge of this subject, it is desirable, nevertheless, if only for the purpose of stimulating new lines of thought and research, to review critically the available facts and to add certain original data bearing upon the problem. Such an analysis has formed the basis for the present concept which suggests a rational explanation of this enigma on the basis of our present state of knowledge.

The Physiology of Lymphopoiesis

Reference to chart 1 shows schematically the course of events in the evolution of the lymphocyte from the mesenchymal rest, the non-phagocytic reticulum cell, through the phases of maturation to the definitive small round cell readily identified wherever found as the lymphocyte. While it is believed that all of the primitive cells (including the reticulum cells) are totipotential, yet because of the environmental conditions, the conditioning stimuli received, or both, these precursors mature only in the direction of lymphoblasts in lymph nodes and spleen and in a few other locations. All cells below level 2 are fully differentiated units and appear to have lost their power to reproduce cells other than lymphocytes. As indicated by the chart, lymphopoiesis is usually effected by progressive stages of maturation and division (chiefly mitotic) through the successive levels 1, 2, and 3, the latter level being most active (quantitatively) under physiologic and certain pathologic conditions. However, lymphopoiesis may also be effected to an imporant degree by a rapid division of cells in level 4 (chiefly amitotic). The qualitative characteristics of these cell types have been described previously in detail.[2, 3]

The significance of the histologic structure of the lymph nodes in which these changes take place has long been a subject of controversy. The pioneer hypothesis of Flemming [4] which emphasized the significance of the so-called germinal center, though contested by Marchand,[5] Hellmann,[6] Heilmann,[7] Latta,[8] Heiberg,[9] Pol,[10] and many others, has been vigorously supported by the work of Aschoff,[11] Groll and Krampf,[12] Maximow,[13] et al. At present the prevailing opinion supports Flemming's original concept of the import of the secondary nodule. Original work in this laboratory has indicated

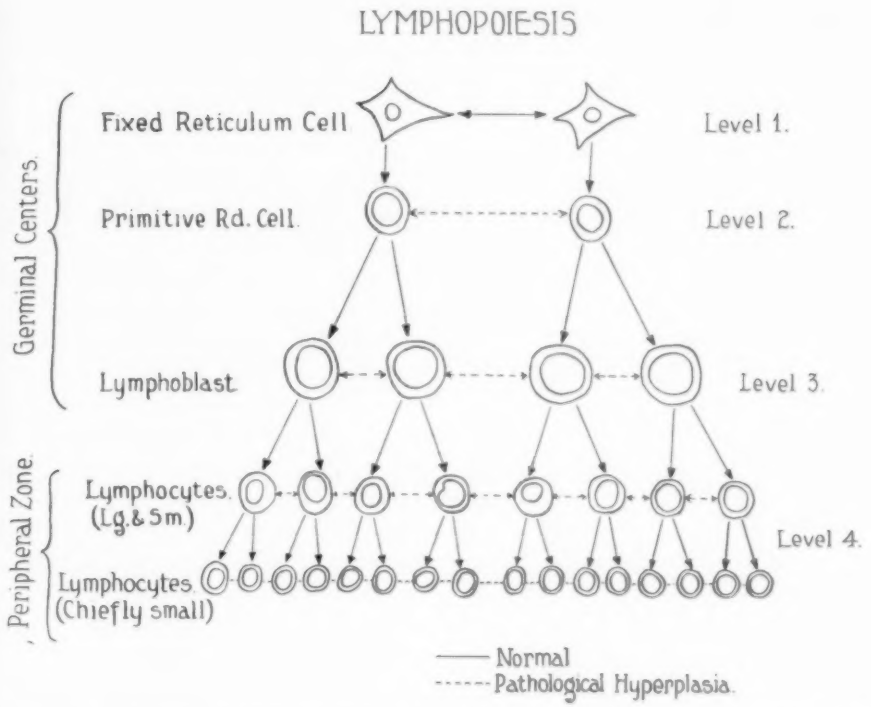

CHART 1. A graphic representation of physiologic and pathologic lymphopoiesis. The cells, in their relationships to normal physiologic lymphocyte production, are shown by connecting them with solid lines. The non-phagocytic reticulum cell gives rise on the one hand to daughter reticulum cells and on the other, by maturative phases, to primitive round cells and thence to lymphoblastic units. Further division and maturation of the latter elements result in the production of the mature cells of the peripheral zone, which not only encircle the germinal centers but also are diffusely distributed throughout the lymph node. Normally most of the proliferation occurs by concomitant maturation and division. However, in the pathologic states of leukemia and lymphosarcoma, it is suggested that division is accentuated and maturation is limited. Various degrees of maturative arrest result in production of the cells of various levels of immaturity as seen in different cases of these diseases. This is indicated by the horizontal dotted connecting lines indicating proliferation with minimal maturation. It is clear from this chart that, theoretically, pathologic proliferation with maturation arrest may be either neoplastic in nature, or metabolic in the sense that unknown disturbed physiologic factors permit or cause undue proliferation without concomitant maturation.

that intense stimulation of the formation of lymphocytes results in a proliferation of the germinal center tissue which breaks through the limiting zone of small lymphocytes and may eventually almost completely fill the entire node within the capsular borders. As this tissue extends through the node it becomes mixed more and more with cells of level 4, so that its identity becomes less and less clearly defined, until in the completely hyperplastic node the entire content of the structure reveals only a diffuse lymphatic tissue with a thorough mixing of all the various types of lymphocytes. Lymph nodes with small but prominent germinal centers are probably resting structures. This would account for the histologic differences between the peripheral deposits of lymphatic tissue which contribute only slightly to the

mass of circulating lymphocytes and those deposits about the gastrointestinal tract which are continually being stimulated by afferent streams from the gut and which, by their efferent vessels, supply nearly all the blood lymphocytes.[14, 16]

Chart 1 shows that when normal maturation and division both occur, lymphopoiesis is expressed histologically by the prominence and extension of the tissue represented in levels 1, 2, and 3, i.e., by the germinal center tissue of Flemming. It indicates, however, that abnormal proliferation is theoretically also possible by specific multiplication without maturation of the cells at any of the levels shown, since all of these cells have the power to reproduce themselves. It is further evident that neoplastic changes may occur at any of the stated levels and thus provide a third mechanism for the over-production of lymphocytes. Each of these three mechanisms may conceivably give rise to pathologic states characterized by proliferative phenomena. The significance of these potentialities will become clear in the later discussion of certain of these pathologic states.

A study of the blood and tissue changes occurring in infectious mononucleosis serves to emphasize the orderly course of events which occurs when the stimulus to increased production of lymphocytes as provided by this infection is pronounced. Chart 2 records the significant hematologic observations made upon patient H. W. from the time he came under observation (24 hours after the onset of the disease) until the blood findings returned to normal. The lymphocytes, polymorphonuclear leukocytes and monocytes, classified by the supravital technic, are shown in absolute numbers together with the totals for white and red cells. In the lower block are plotted the values in per cent for the young lymphocytes as determined in Wright-Giemsa stained blood films, classification being made according to the principles outlined in an earlier publication.[2] It will be observed from a study of this chart that whenever the total lymphocytes exceed the normal number for an individual in health, the percentage of young types is distinctly above the upper limit of normal (over 10 per cent). It is also clear that as the total number of lymphocytes in the peripheral blood fluctuates, there is a corresponding and parallel fluctuation in the percentage of young forms. This is shown especially well during the repeated observations made on Dec. 5, when a study of the blood was made every 15 minutes for three hours. These facts indicate that delivery of increased numbers of lymphocytes to the blood is attended by an increasingly marked shift to the left in this series of cells and bespeak the origin of the cells from a series of maturative phases involving the increased activity of germinal centers, as indicated in chart 1 for levels 3 and 4.

Further evidence for this belief is secured by an examination of the pathological tissue in cases of infectious mononucleosis. A cervical node was obtained Dec. 6 by biopsy from a patient, C. W. Z., early in the course of the disease. The photomicrographs (figures 1 and 2 in plate 1) show quite plainly the proliferating germinal center tissue infiltrating the

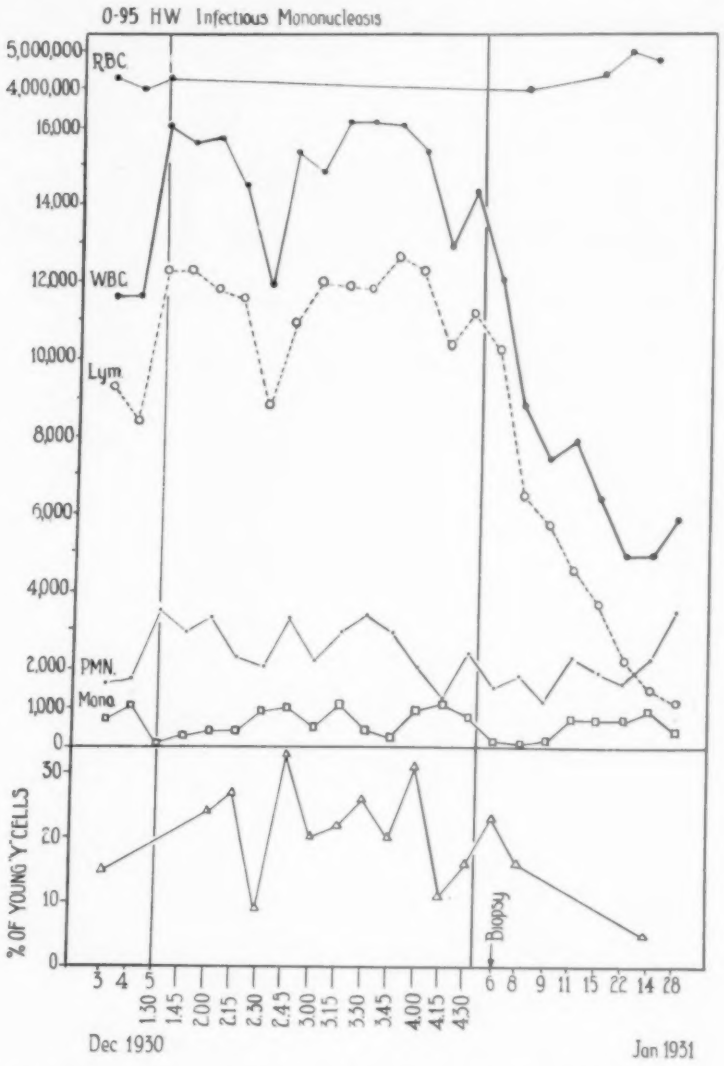

CHART 2. Blood findings obtained by study of case H. W. who had infectious mononucleosis. Serial 15 minute counts were made during the period indicated on Dec. 5, 1930, and the percentage of young lymphocytes charted to contrast with the fluctuation in total numbers of lymphocytes. The correlation between increase in young cells and increase in total numbers is evidence that lymphopoiesis is physiologic as described on chart 1. Tissues from this case shown on plate 1, figures 3 and 4.

entire gland to such an extent that the greater portion of the node is composed of pre-lymphoblastic units, indicating that the supply of lymphocytes is obtained by increased activity and functioning volume of the germinal center tissue of Flemming. The lymph node from patient H. W. was removed late in the course of the disease, just prior to the restoration of the lymphocytes to normal levels (chart 2). The microscopic character of the

tissues is now totally different (figures 3 and 4 in plate 1). The sections clearly show that "pure" germinal center tissue is much less obvious, the mixing of the cells in the lymph node is more uniform, and increased numbers of more mature lymphocytes are especially prominent. These observations suggest that lymphocytes are being matured by the process indicated in chart 1. It is also pointed out that during the course of these events the predominating cell in the peripheral blood is the young, but not pathological, lymphocyte, corresponding to cells of the level of chart 1 labeled "large lymphocytes." It is felt that these facts constitute strong supporting data for the theory of Flemming and indicate the essential truth of the course of events in normal physiologic lymphopoiesis shown in chart 1. The importance of these observations will become more apparent in the subsequent consideration of lymphopoiesis in the non-infectious hyperplastic lymphatic states.

The normal physiologic stimulus for lymphopoiesis has not as yet been determined. Experimental procedures, such as light,[17, 18] heat,[19] roentgen-ray,[20, 21] fat diets,[22] extirpation of the spleen [23, 24] and parenteral absorption of foreign proteins,[25] have all been shown to influence the peripheral level of lymphocytes, but none of these have been shown to be important in the physiologic or pathologic production of lymphocytic hyperplasias.

Equally obscure is the important selective mechanism by which certain lymphocytes are retained in the mother tissues and others are released to the lymph stream. It is clear that any intelligent attack upon the problem of the mechanism of production of the lymphatic dyscrasias is hampered by our lack of knowledge of these two fundamental physiologic processes.

The Pathology of Lymphopoiesis in Non-Infectious States

Although earlier investigators, particularly Haller,[26] had described whole blood which had the gross appearance of pus, it remained for Virchow [27] and

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Plate 1

Photomicrographs of paraffin sections of lymph nodes obtained by biopsy from cases of infectious mononucleosis and stained with hematoxylin and eosin.

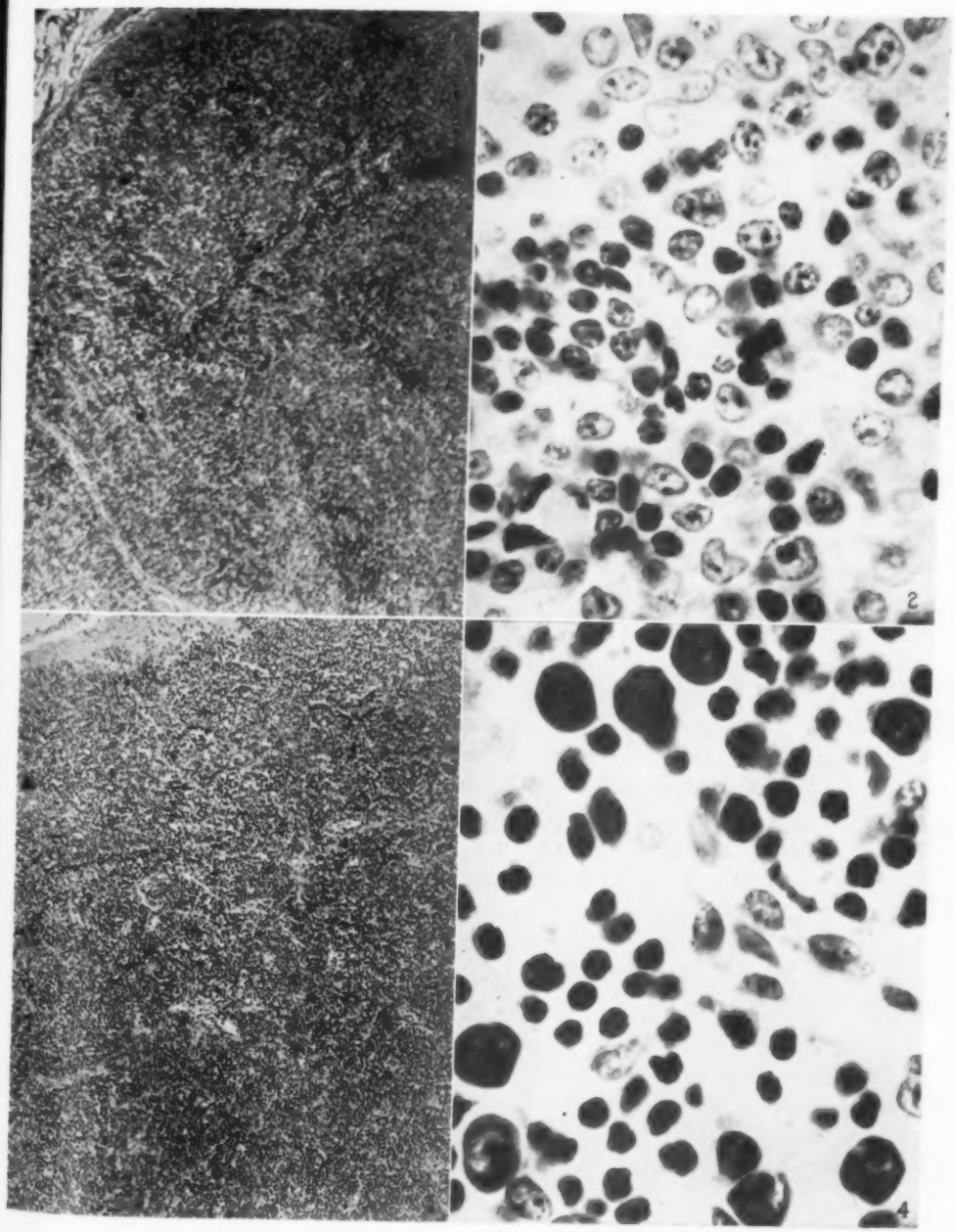
Fig. 1. *Case C. W. Z.* Low power view of a section through the cortex of the node. The capsule is seen in the upper left hand corner. Note the pale staining germinal center tissue which has invaded the entire node and is in direct continuity with the ill-defined secondary (germinal center) nodule seen in the upper center of the photomicrograph. This tissue was removed *early* in the course of the disease.

Fig. 2. *Case C. W. Z.* Oil immersion view taken through the edge of the secondary nodule referred to in the description of figure 1. The invasion of the peripheral zone of small lymphocytes (center of photograph) by germinal center tissue (upper part of photograph) is clearly shown. Mature lymphoid elements are in the minority.

Fig. 3. *Case H. W.* Low power view of a section through the cortex of the node. This tissue was removed *late* in the course of the disease. The germinal center tissue is less prominent and is evenly mixed with the more mature cells of the node. Mature units now greatly outnumber the primitive cells and secondary follicles can no longer be delimited.

Fig. 4. *Case H. W.* Oil immersion view taken from the same section as figure 3. The view is representative of all portions of the section. Note the predominance of matured cells as compared with figure 2, above, and the corresponding decrease in primitive-cell units. Large lymphoblasts with heavily basophilic cytoplasm and large prominent nucleoli are now particularly abundant. A vessel runs through the center of the section.

PLATE 1.



Bennet [28] first to interpret correctly this phenomenon as characteristic of leukemia. John Bennet in 1845 described a case with autopsy report in which death took place from " the presence of purulent matter in the blood." Bennet recognized the non-inflammatory character of the mechanism by which it was produced, but he believed that the white corpuscles arose in a " blastema formed of liquor sanguinis " and did not divorce his theory entirely from that of suppuration. Virchow, however, immediately recognized his discovery as a new disease, " White Blood," emphasized its unique nature and cautiously suggested as the possible mechanism a diseased spleen which transformed red blood cells into white ones. In a later communication,[29] Virchow classified the diseases characterized by lymphatic hypertrophy into four groups: 1, leukemic lymphoma (lymphatic leukemia); 2, simple hyperplastic lymphoma (probably a mixture of pseudoleukemia and leukosarcoma); 3, lymphosarcoma, soft form (lymphosarcoma); and 4, lymphosarcoma, hard form (Hodgkin's disease). Virchow therefore laid the foundations for a clinico-pathologic classification of the idiopathic lymphatic hyperplasias which, with minor changes and amplifications, has held to the present day. Cohnheim,[30] using the term pseudoleukemia, separated from Virchow's soft form of lymphosarcoma a lymphatic state in which the gross and microscopic tissue changes of lymphatic leukemia were present but without the blood changes. Kundrat [31] further clarified this group by his observation of cases in which the disease, originating in an isolated single lymphatic node, became locally invasive and later metastasized by way of the regional lymphatics. Finally Sternberg [32] in a monumental contribution, the importance and significance of which has not been generally recognized, differentiated a group of cases of lymphosarcoma which started locally as an invasive tumor mass but which eventually became leukemic in that the abnormal cells composing the growth gained entrance to the blood stream causing a leukemia of the large cell type. Virchow's fourth group (Hodgkin's disease) is now generally regarded as primarily an infectious granuloma.[33] The observations of Sternberg,[34] the recent studies by L'Esperance in Ewing's laboratory,[35] as well as observations and experiments from our own laboratory tend to implicate the tubercle bacillus rather than other bacteria [36] or viruses [37, 38] as the initial causative agent.

This view of Hodgkin's disease is not, of course, necessarily in conflict with the fact that certain cases exhibit definite neoplastic characteristics. The phenomena of neoplasia arising in chronic lesions is not unusual in other tissues of the body. When neoplastic transformations occur in lymphoid tissues, however, the cell primarily involved is definitely not the lymphocyte, as suppression of lymphopoiesis with lymphopenia is an outstanding feature of the disease. Unpublished studies in our laboratory make it probable that either the reticulum cell, the monocyte or both are the elements in lymphatic tissue that undergo the characteristic pathologic changes. Hodgkin's disease, therefore, while a disease of lymphatic tissues, does not appear primarily to affect the lymphocyte itself and hence is not discussed further in this paper.

It is clear, therefore, that, with the exception of the separation of Hodgkin's disease from the group of primary lymphatic hyperplasias, little advance has been made toward an understanding of this group of diseases

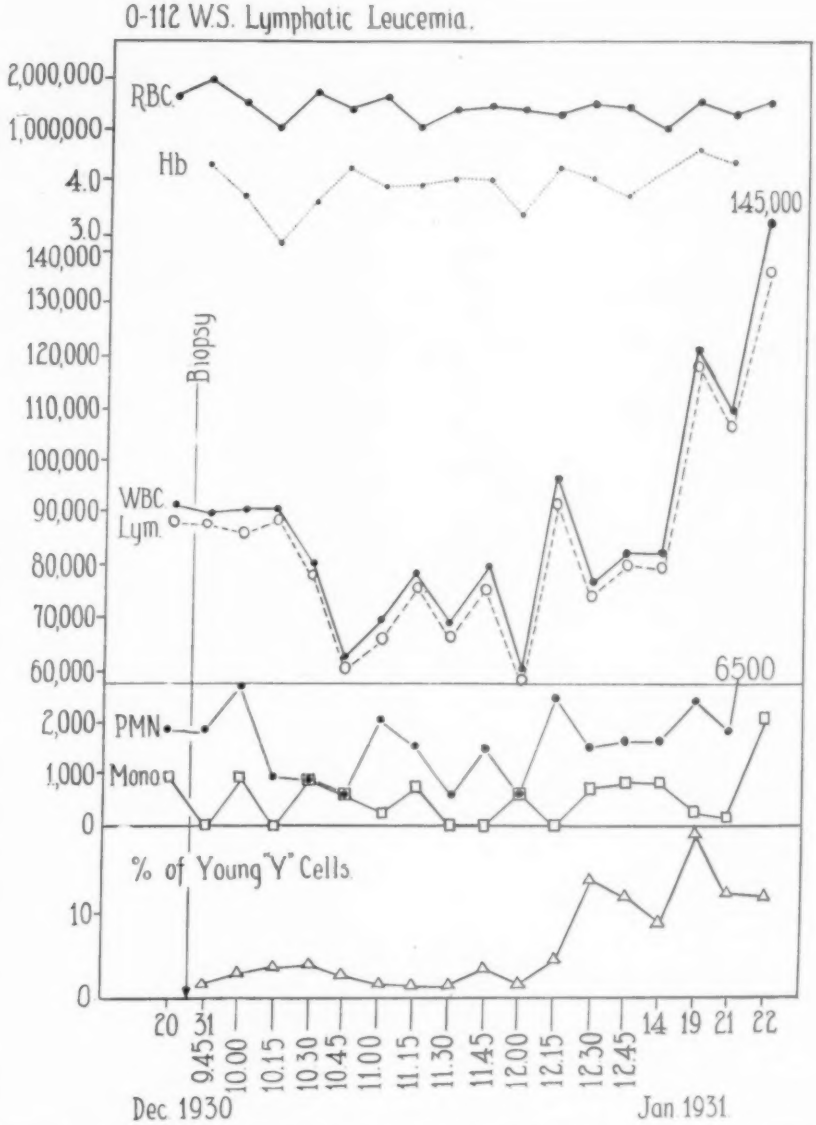


CHART 3. This graph shows the result of the blood findings in case W. S. who had lymphatic leukemia. Serial 15 minute counts during the period indicated do not show parallel fluctuations in "young" cells (as classified by maturative criteria shown to be valid for normal lymphopoiesis) and total numbers. From Jan. 14 to 22 there was a rise in these "young" types but not in proportion to the rise in the totals. It is believed that these facts suggest that increase in proliferation of lymphocytes in this disease is marked by the production of cells which do not exhibit the maturative characteristics seen in cells produced by physiologic lymphopoiesis. Tissue from this case shown on plate 2, figure 1.

since Sternberg's significant contribution in 1908. We have today then four clinico-pathologic states which are characterized by lawless proliferation of the lymphatic type of cell: viz., lymphatic leukemia, lymphatic pseudo-leukemia, leukosarcoma, and lymphosarcoma. By a critical analysis of typical cases from each of these classes we shall trace certain facts which apparently help to explain the mechanism responsible for lymphatic leukemia and which, at the same time, suggest a relationship of each of these lymphatic dyscrasias to the others. Cases in addition to those cited have been studied with entirely similar findings and conclusions. To conserve space, only data relevant to this discussion will be given.

Chronic Lymphatic Leukemia

Case W. S. This patient, a white male, aged 52 years, first came under our observation on Dec. 20, 1930. He gave a history of general glandular enlargement, increasing pallor, and dyspnea of three years' duration. No history of a primary local lymph node enlargement could be obtained. Physical examination showed, in addition to the generalized adenopathy, an enlarged spleen, the border of which reached the level of the umbilicus. The enlarged nodes were elastic to the touch, freely movable, discrete and not painful on pressure. The blood examination showed the presence of pathologic lymphocytes in increased numbers, as shown in chart 3. These lymphocytes were all of the small round type, uniform in size, and each possessed a very narrow rim of cytoplasm containing small spherical (not rod-like) mitochondria about a nucleus that exhibited a characteristically heavy chromatin cloud and occasionally a small nucleolus. Studies of the delivery of the young lymphocytes, classified according to standards of proved value in appraising normal lymphopoiesis, failed to show during the serial 15 minute interval studies of Dec. 31 any correlation between germinal center activity and intensity of lymphopoiesis (chart 3), in sharp contrast to the findings in infectious mononucleosis (chart 2). It is also clear from chart 3 that although the lymphocytes ranged between 60,000 and 90,000 on Dec. 31 (from 9:45 a.m. to 12:00 noon), at no time during this interval did "young" cells constitute more than 3 per cent of the total.

Plate 2

Photomicrographs of paraffin sections of lymph nodes removed at biopsy and stained with hematoxylin-eosin, oil immersion views. Figure 1 (chronic lymphatic leukemia) is to be contrasted with figure 2 (pseudoleukemia). Figure 3 (leukosarcoma) is to be contrasted with figure 4 (lymphosarcoma). The cells of figures 1 and 2 are morphologically identical; similarly identical are those of figures 3 and 4. Note, however, the vast differences between the cells of figures 1 and 2 and those of figures 3 and 4.

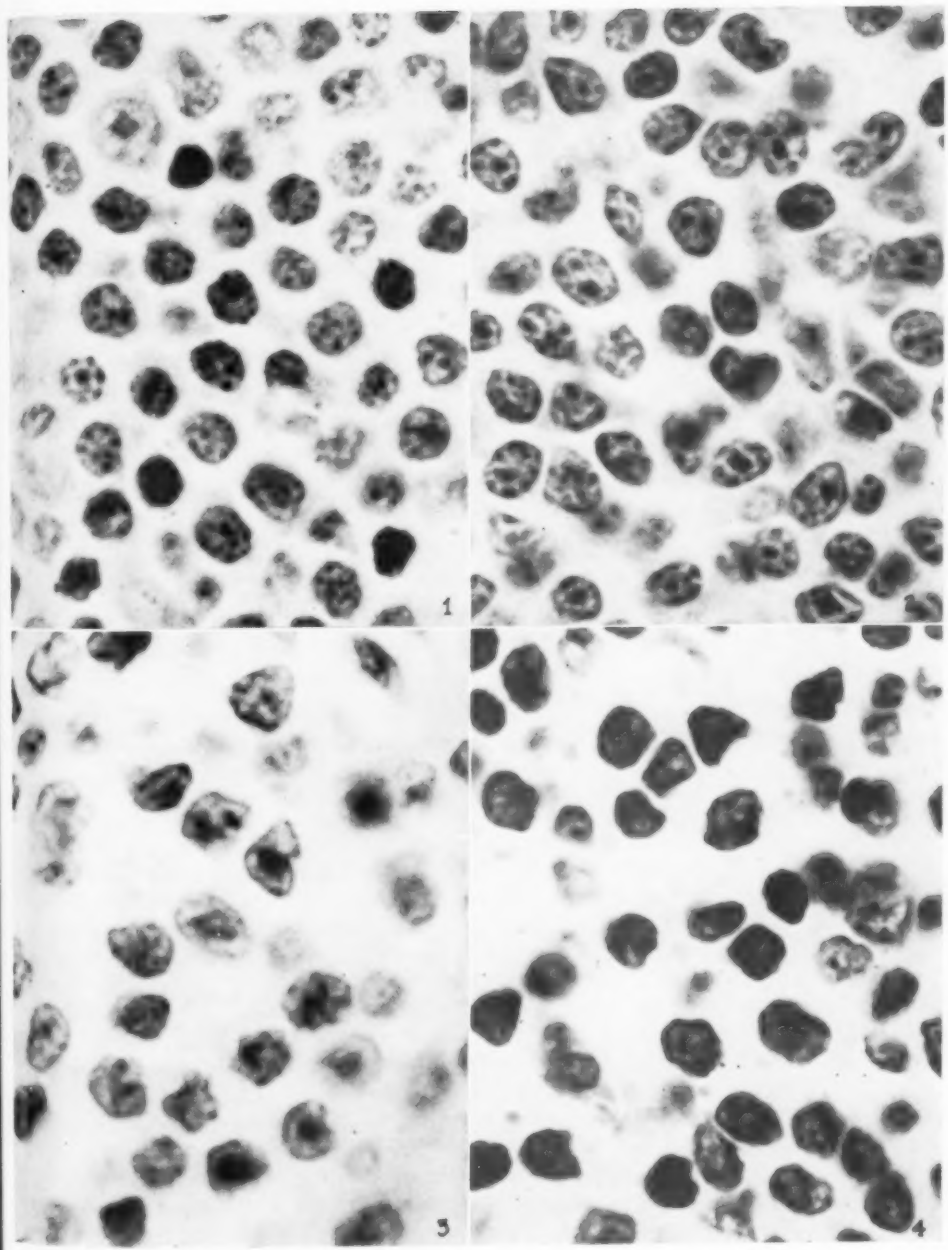
Fig. 1. *Case W. S. Chronic lymphatic leukemia.* Note the endless reduplication of one type of cell with heavily chromatic nucleus and small but prominent nucleolus. The cells tend to be uniform in size and shape. No mitotic figures were found in this section, and there was no tendency to invade the capsule.

Fig. 2. *Case R. D. B. Lymphatic pseudoleukemia.* The morphologic characters of the cells in this section were identical with those of figure 1.

Fig. 3. *Case E. M. Leukosarcoma.* These cells vary greatly in size and shape, tend to be vesicular and do not have the characteristic chromatin structure of those shown in figures 1 and 2. Mitotic figures were plentiful in this section. This tissue showed definite invasive characteristics and invaded the surrounding structures by direct extension. (See figure 1.)

Fig. 4. *Case F. M. Lymphosarcoma.* These cells correspond in all particulars with those shown in figure 3. Mitotic figures were particularly rich in the section from this patient, and the tissue was locally invasive.

PLATE 2.



The obvious conclusion is that the lymphopoiesis of chronic lymphatic leukemia is not of the normal germinal center type. This fact, in conjunction with the observations that the cytoplasm of the immature cells is often relatively deficient in basophilic substance, and that the cells tend to divide by amitosis (mitotic figures are a great rarity in the blood and in sections of tissue from chronic lymphatic leukemia), suggests that multiplication of cells in this disease is chiefly by amitotic division with *minimal maturation*. In Chart 1 this would be indicated by proliferation of cells in a horizontal direction with very little progressive development vertically; that is to say, very little multiplication *with* maturation. It is clear that this hypothesis would account for small cell (chronic) leukemias as well as for the more acute large cell types, the difference being dependent upon the cell level at which the abnormal proliferation took place. It will be recalled that, physiologically, lymphocytes multiply at the various levels with some maturation arrest, but normally the reserve of cells at each stage remains small at any one time, the majority maturing promptly. In chronic lymphatic leukemia it would seem that this normal physiologic equilibrium is reversed so that division *with* maturation is quite small and division without maturation is correspondingly large. The end result is an overproduction of immature cells of no functional value to the body. In this respect the mechanism is similar to that observed in the over-production of megaloblastic tissue in pernicious anemia. An alternative theory in explanation of the horizontal proliferation of lymphocytes at immature levels in lymphatic leukemia is one which would link the mechanism with a neoplastic alteration. This hypothesis will be considered in the discussion of leukosarcoma.

Lymphatic Pseudoleukemia (Cohnheim)

Case R. D. B. This patient, a white male aged 64, first came under observation on Dec. 13, 1933, complaining only of generalized lymph gland swelling. Physical examination added only the fact that the spleen was enlarged to the costal border. The lymph nodes varied in size from a pea to a walnut and had exactly the same characteristics as described for patient W. S. above. Biopsy was performed with removal of a left cervical node on Dec. 20, 1933. Both supravital examination and the study of fixed paraffin sections revealed hyperplasia with metaplasia of the lymphatic elements, indistinguishable from the tissue changes seen in classical chronic lymphatic leukemia and identical with the tissue from patient W. S. (Compare on plate 2 photomicrographs 1 from the tissue of W. S. and 2 from the tissues of R. D. B.) The hematologic examination showed *absolutely no abnormalities* either in the quantitative values or in the qualitative characteristics of any of the circulating cell types. All lymphocytes were of the normal types, although repeated studies with both the supravital and fixed technics were utilized in an effort to detect pathologic variations. Chart 4 is a graph of the cellular equilibrium prevailing in this patient and shows that for the 25 months he has been under our observation no leukemic tendency has been observed. Roentgen-ray therapy in suitable dosage has been applied to the superficial glandular swellings as indicated on the chart in order to control the local enlargements. Throughout, this patient has been in the best of health and has continued to fulfill his occupation as a railroad crossing watchman.

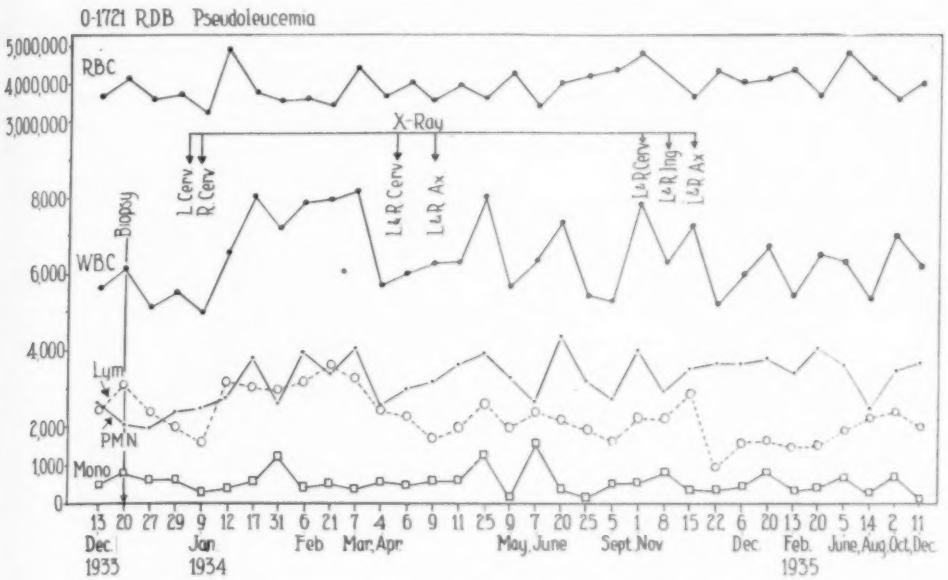


CHART 4. Results obtained by blood examination of patient R. D. B. who had lymphatic pseudoleukemia. No abnormalities, either qualitative or quantitative, have been observed during the period of two years shown on this chart. Examination of a lymph node removed at biopsy on Dec. 20, 1933 showed a histology indistinguishable from that of patient W. S. (chart 3) who had lymphatic leukemia with marked lymphemia. Local roentgen-ray treatments were given, as indicated on the chart, for the sole purpose of reducing the local swellings of the lymph nodes. Tissue shown on plate 2, figure 2.

From the facts as herein outlined the type of lymphatic hyperplasia is undoubtedly identical with that found in chronic lymphatic leukemia. In this patient, R. D. B., however, the barriers that allow only normally matured cells to gain entrance to the lymphatics and thence to the blood stream are effective in screening out the leukemic unmatured types, thus confining them to the lymphatic tissues, whereas in the former case (W. S.) this mechanism has failed. The absence of leukemic cells in the peripheral blood in case R. D. B. has resulted in an absence of infiltrative phenomena (large liver, anemia, etc.), as normal lymphocytes merely divide, mature and die and are not capable of endlessly dividing without maturing. Hence, unlike leukemic cells, normal lymphocytes do not crowd out, " infiltrate " and replace other tissue cells. It is clear that patient R. D. B. is in good health and will continue so, as long as the leukemic cells do not gain entrance to the blood stream. That this screening mechanism may become ineffective at any time, thus converting the disease into a true leukemia, has been observed by others.[39, 40]

LEUKOSARCOMA (STERNBERG)

Case E. M. This patient, a white child, aged 20 months, came under our observation Febr. 11, 1935, eight weeks after the first evidence of the beginning of her illness. Pallor, dyspnea and generalized glandular enlargement with splenomegaly

developed rapidly. A careful history revealed that the first enlargement which appeared was a lump in the left submaxillary region. After a period of about four weeks there was an increase in the size of the spleen with a simultaneous enlargement of the lymphatic structures. A blood count six weeks before admission was said to have shown 35,000 white blood cells with the majority "mononuclear" leukocytes. Deep roentgen-ray therapy was applied over the mediastinum to relieve the dyspnea and reduce the number of cells. A careful hematologic examination made upon our first contact with the case revealed the classical findings of lymphatic leukemia with the one exception, that upon supravital examination it was possible to discriminate, after careful study, between two morphologically distinct types of lymphocytes existing side by side in the blood films. The one type was found not to depart from the normal in any recognized morphologic particular. The second type of lymphocyte

TABLE I

Important Supravital Criteria of Three Biologic Classes of Lymphocytes

Class	Characteristics of nucleus				
	Visible nucleoli	Chromatin distribution	Shape	Relative size of nucleus to cell	Nuclear membrane
Normal mature cell	Not prominent	Heavy cob-web	Varies	Varies	Sharp
Leukemic cell	Prominent	Heavy splotches	Offer bizarre	Tends to be large	Sharp
Sarcoma cell	Large	Fine cob-web	Round	Large	Indistinct

Class	Characteristics of cytoplasm			
	Quality	Neutral red vacuoles	Refractive vacuoles	Mitochondria
Normal mature cell	Faint yellow	Rose-red if present	None	Large rods or spheres
Leukemic cell	Limpid clear	Largely absent	None	Small spheres
Sarcoma cell	Faintly grey	1–10 highly refractive vacuoles about periphery of nucleus. Deep scarlet when stained.		Dust-like

Class	Other characteristics of cell			
	Motility	Approximate size	Phagocytosis	Fragility
Normal mature cell	Present	95% less than 9 microns	Absent	Slight
Leukemic cell	Absent	Varies	Absent	Marked
Sarcoma cell	Absent	12–14 microns	Absent	Moderate

present was definitely abnormal but differed from the normal in details other than those previously described as characteristic of the cells in chronic lymphatic leukemia. These pathologic cells ranged in size from 8 μ to 15 μ, the majority being similar in size to the normal intermediate lymphocyte. The cytoplasm consisted of a narrow rim about the nucleus with a moderate sprinkling of dust-like mitochondria and contained from one to a dozen vacuoles which either did not stain at all or else took the vital neutral red with a reaction strongly to the acid side of its indicator range. The nucleus of this atypical cell was vesicular and contained a fine web-like chromatin

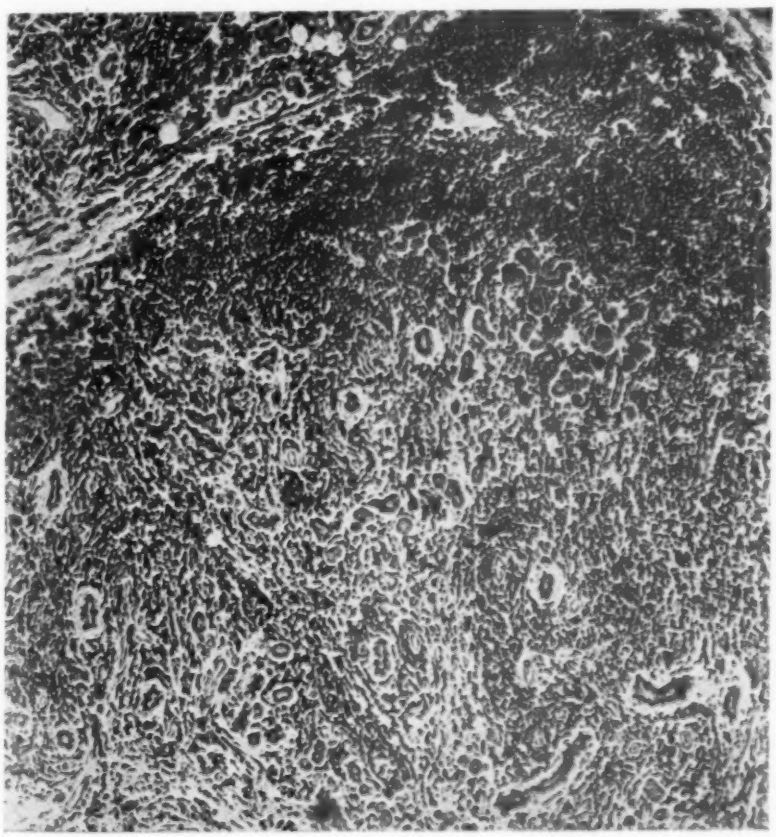


FIG. 1. *Case E. M. Leukosarcoma.* Low power view through submaxillary salivary gland adjacent to submaxillary lymph node. A portion of the lymph node lies in the upper right hand corner. The capsule of the node has been destroyed, and the lymphocytic elements have invaded by direct extension the submaxillary gland in the center and lower part of the section.

with a rather large nucleolus. The nuclear membrane was indistinct so that not infrequently there was some difficulty in sharply delimiting the area occupied by the nucleus. This cell we have called the "sarcoma cell" to distinguish it from the other types of lymphocytes described. Morphologically, in supravital preparations it is similar to proved sarcoma cells found in round cell sarcomata of the connective tissues. Table 1 by description compares this with the other lymphocytes mentioned in this paper.

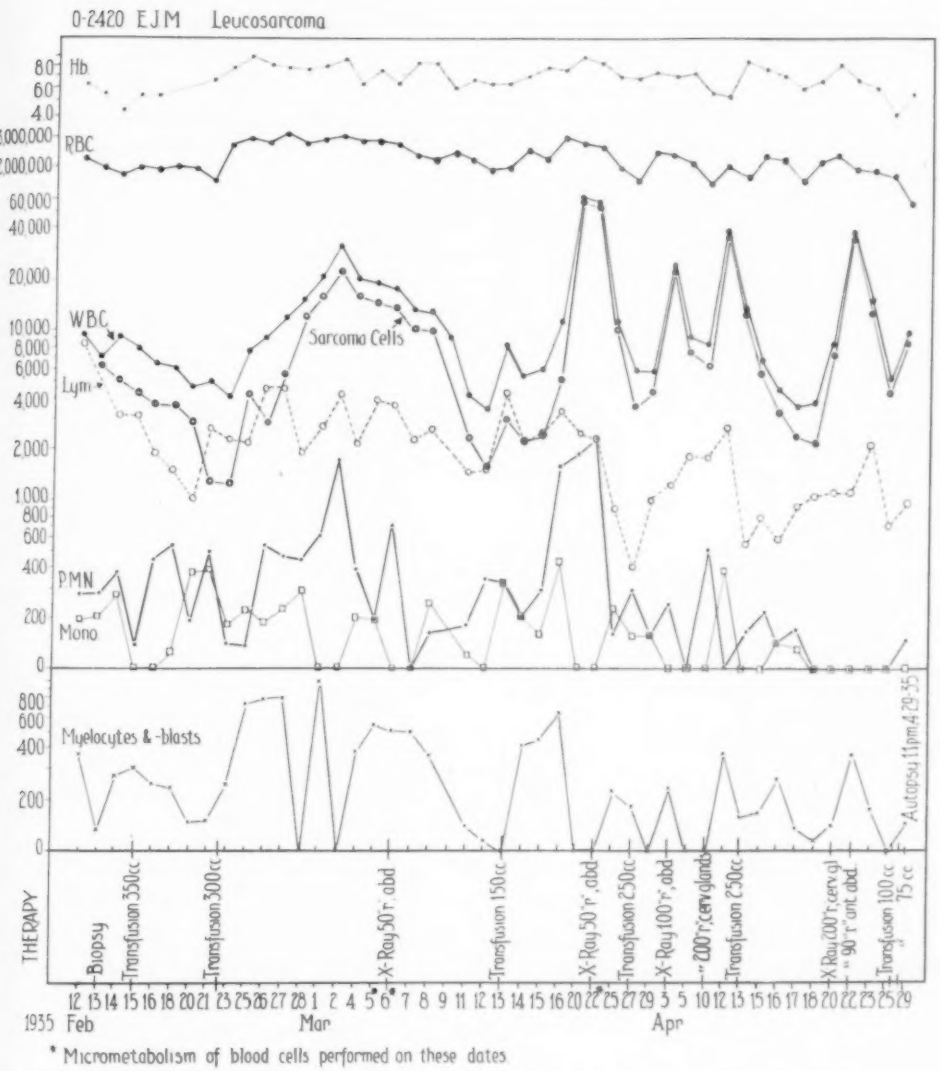
The lymph node, removed at biopsy from the submaxillary region, differed

markedly from those found in the usual case of lymphatic leukemia. The lymph node could not be removed with capsule intact, as it was bound to the surrounding tissue. Upon cut section, the contents of the node were gray in color, extremely soft in consistency and very cellular. Supravital examination of scraping of this material showed a mixture of normal lymphocytes and cells corresponding to those found in the peripheral blood and designated as "sarcoma cells." Mitotic figures among the latter were very frequent. Paraffin sections showed characteristic sarcoma tissue. Remnants of secondary nodules were invaded and destroyed by these abnormal cellular elements. The proliferative process had broken through the capsule and invaded, in typically neoplastic fashion, by direct extension, the adjacent parenchyma of the submaxillary gland. Figure 1 shows the characteristic invasiveness of these cells.

Chart 5 depicts graphically the course of the hematologic events as they occurred in this patient. In this chart the sarcoma cells are shown by the circles connected with a solid line, and the normal lymphocytes are shown by the circles connected with a dotted line. Several points on this chart are of interest and of importance to the theory of the mechanism of production of leukemia and will be discussed to the exclusion of other interesting data shown but not vital to the tenets of this paper.

It is clear that the excess of white cells consists entirely of the "sarcoma cell type" of lymphocyte, the curve representing the total leukocytes paralleling that representing the sarcoma cells. The curve for the normal lymphocytes constitutes a virtual plateau fluctuating for the most part between 2,000 and 4,000 cells and deviating downward from this level only once, when the sarcoma cells were at a very high level (60,000). This fall in the number of normal lymphocytes was probably due to a suppression of multiplication in the tissues (infiltrative phenomena) and not to a roentgen-ray effect, as it will be observed that a considerable drop in the red blood cells occurred at the same time, and that larger doses of roentgen-ray were given both before and subsequent to this fall without disturbing the level of either normal lymphocytes or red cells. It is also clear from this chart that the two kinds of lymphocytes shown have a quite marked difference in susceptibility to the destructive effects of the roentgen-ray (note in particular the behavior of these two cells to the treatment given on March 6). This further substantiates the biologic difference between them suggested by their morphologic characteristics. It is also evident that the extraordinary radiosensitivity of these sarcoma cells, transcending considerably even that of the normal lymphocytes, tends to place these cells in the category of neoplastic cells of lymphoid origin.

From the foregoing it would appear probable that the leukemia observed in patient E. M. is a type of lymphatic leukemia which differs from those already mentioned in at least three important respects: 1, in the morphologic characteristics of the abnormal lymphatic elements; 2, in their relative radiosensitivity; and 3, in the histo-pathology of the affected lymphatic tissues. These points all indicate a mechanism responsible for the leukemia of leukosarcoma which is different from that of simple lymphatic leukemia. This mechanism, as clearly indicated by the facts recited, points strongly to a neoplastic alteration of lymphopoiesis. This malignant lymphocyte then invades the blood stream (causing "leukemia") and infiltrates the various tissues of the body, giving rise to a clinical and



* Micrometabolism of blood cells performed on these dates

CHART 5. Blood findings in patient E. J. M. who had leukosarcoma. Particular attention is directed to the charting of two types of lymphocytes, one labeled "sarcoma cells" and the other "lymphocytes." The charting is upon semi-logarithmic scale. The normal lymphocytes at no time greatly exceed in numbers the value regarded as normal for the average person in health. The "sarcoma cells," however, between the periods in which roentgen-ray therapy was applied rise to high values, independently of the normal lymphocytes. The effectiveness of small doses of roentgen-ray in reducing the number of sarcoma cells and the relatively ineffectual results of these doses upon the normal lymphocytes are clearly shown and bespeak further for a biologic difference between these two types of lymphocytic cells. Tissues shown as figure 1 and also on plate 2, figure 3.

pathological picture simulating ordinary lymphatic leukemia. This mechanism exemplifies the third type of lymphocytosis which is theoretically possible according to the chart presented in the discussion of physiologic lymphopoiesis.

Lymphosarcoma (Kundrat)

Case F. M. This patient was a white male, aged 60, who was found to have "lumps" in his abdomen five months prior to the present observations. Physical examination on Febr. 2, 1931 showed generalized swelling of the lymph nodes, including the mesenteric nodes. The nodes were discrete, rather hard, freely movable in some cases and fixed in others, but all were without tenderness to pressure. The spleen was enlarged to 5 cm. below the costal border, and there was fluid in the abdomen. Gastrointestinal roentgen-ray series as well as other studies were negative. Repeated examinations of the blood showed no evidence of leukemic changes, either from a quantitative or qualitative standpoint (chart 6 shows two counts taken

F.M. Lymphosarcoma

	2–4–31	2–26–31	8–3–31
R.B.C.	3,900,000	3,530,000	3,260,000
W.B.C.	7,600	4,200	5,800
P.M.N.	4,864	2,604	3,132
Lym.	1,292	966	1,392
Mono.	1,368	588	1,160

Chart 6. Three blood counts taken on patient F. M. who had lymphosarcoma. These were typical of the many observations that were made. No evidence of leukemic change is noted. Tissue shown on plate 2, figure 4.

early in the course of his disease and one near the end, typical of many that were made). Biopsy examination was made on Febr. 3, 1931, and a lymph node 1 by 1 by 1½ cm. removed from the left cervical area. The contents were very cellular, and from the characteristics of the cells examined supravitally a diagnosis of lymphosarcoma was made. Examination of the paraffin sections showed a type of cell histologically indistinguishable from that of the preceding case, E. M. (see plate 2; compare figures 3 (Case E. M.) and 4 (F. M.)).

A review of the pertinent facts in this case, typical of many such that have been observed, shows a lymph gland tumor originating in one part of the body (in this instance in the mesenteric area), which first spread locally and eventually became generalized, probably by metastasis. Clinically and histologically this case was identical with the preceding case (E. M.) except that the malignant cells were not continuously delivered into the circulation, with the result that neither a leukemic blood picture nor the infiltrative phenomena of leukemia developed. That some cases, starting in this manner, at times become leukemic [42, 43] cannot be doubted. In such instances at some time, often following roentgen-ray therapy, the pathological cells undoubtedly gain free access to the blood: that is to say, leukosarcoma develops from the localized neoplastic alteration of the lymphoid cells characteristic of lymphosarcoma.

Aleukocythemic (Aleukemic) Lymphatic Leukemia

From the previous discussion, it may be inferred that there are three forces which determine the number of cells in the peripheral blood. In physiologic lymphopoiesis the level is determined by the balance which

exists between the factors of production, delivery to the blood stream and peripheral loss or destruction. For example, in infectious mononucleosis cases with marked adenopathy but with low total blood counts apparently reflect the existence of a very effective barricade which prevents release of these elements to the lymph and blood streams. This is not the result of high peripheral loss because examination of the cells in the blood stream reveals large numbers of relatively old lymphocytes, a fact which suggests accumulation rather than accelerated peripheral loss.

Careful study of the material accumulated in this laboratory has indicated that, in the diseases characterized by pathologic lymphopoiesis, the factor of peripheral loss of cells is manifested chiefly by tissue infiltration with blood cells, a circumstance which rarely, if ever, occurs to an important degree in the infectious lymphadenopathies.

The withdrawal of enormous numbers of cells from the blood and their storage in the tissue spaces have been outstanding features in some cases in which the blood has shown an actual leukopenia. In fact, in our experience a falling peripheral level of cells in chronic lymphatic leukemia has often been associated with the appearance of signs of heavy tissue infiltration, as shown by roentgen-ray examination of lung fields, an enlarging liver, a developing anemia and thrombopenia, etc. The clinical course, the roentgen-ray studies and the laboratory data in case J. B. illustrate this phenomenon clearly.

Case J. B. This patient, with a peripheral level of cells which averaged 24,000 lymphocytes per cu. mm. of blood for two months just prior to June 15, 1935, had shown no evidences of infiltration (figure 2). The patient then had a spontaneous exacerbation of his disease with total counts rising to an average of 48,000 lymphocytes, with no further changes in the chest roentgen-ray as compared with previous examination. One month after this increase in the cell count occurred, roentgen-ray therapy was given until the peripheral count became stabilized at an average level of 21,000 lymphocytes. This level persisted for 12 days. During the nine days after the establishment of this plateau of 21,000, the count slowly fell spontaneously to an average level of 8,000 lymphocytes. Dyspnea and cyanosis slowly became more evident during the next 17 days, and one month after the spontaneous development of the aleukemic phase, respiratory distress was marked. A roentgen-ray at this time, with a lymphocyte count of 6,083 on Nov. 14, 1935, showed marked infiltration in the right lower lung field. (Figure 3.) This was treated with deep roentgen-ray locally, with some clearing of the cellular infiltration, but without much clinical relief. A roentgen-ray taken 15 days later, Nov. 29, 1935, showed spread of the infiltrative process to the left lung. (Figure 4.) Throughout the aleukemic phase, which persisted 34 days until his death, the lymphocytes maintained an average level of 8,000 cells. There was no increase in size of the lymph nodes during this phase.

This discussion provides an explanation of the mechanism resulting in the so-called aleukemic types of lymphatic leukemia. In some cases with large lymph nodes but low peripheral cell count the " screening " mechanism in the lymph nodes is probably particularly efficient. These cases resemble the pseudoleukemic types exemplified by case R. D. B. previously discussed, the difference being in the relative efficiency of this mechanism. Some

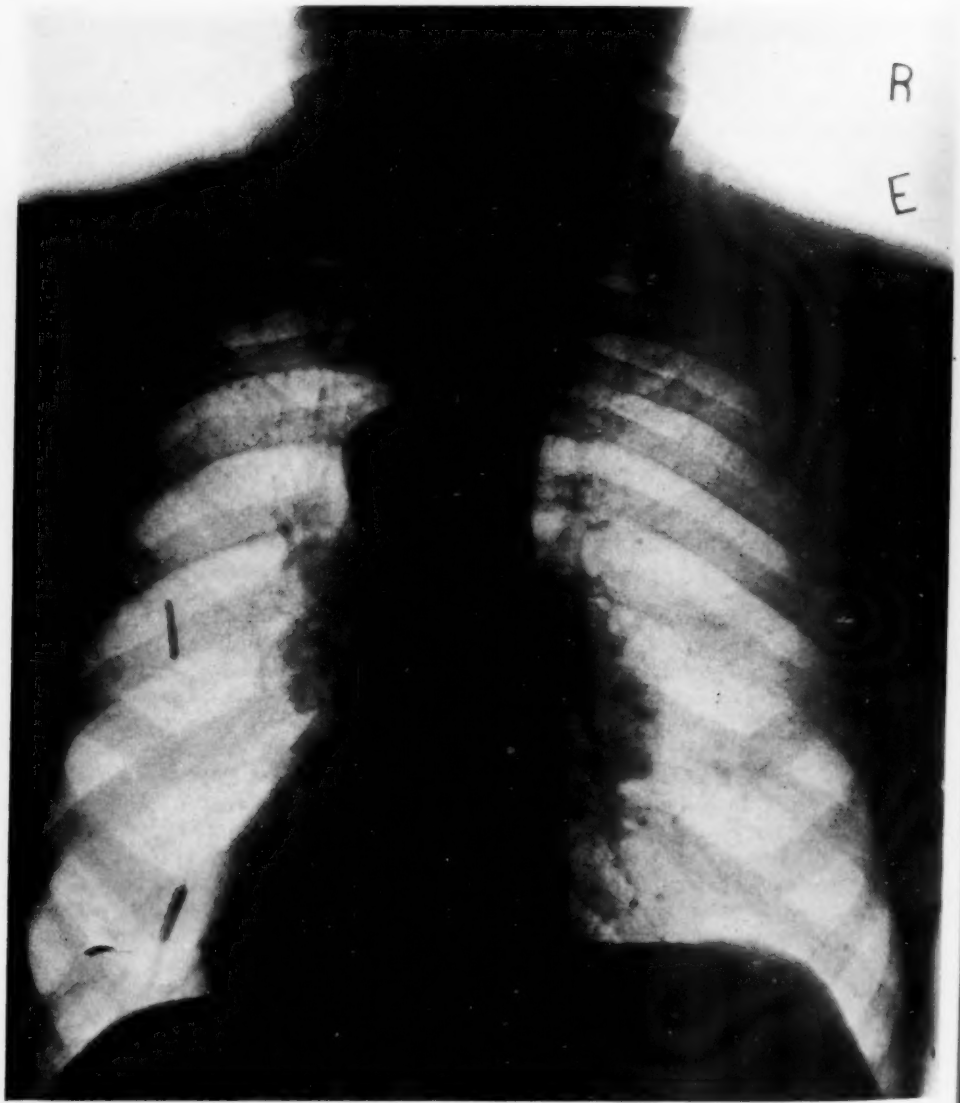


FIG. 2. *Case of J. B. Aleukemic lymphatic leukemia.* Chest plate taken on June 15, 1935. The tracheo-bronchial lymph nodes about the right and left hilus are enlarged, but the lung fields are clear.

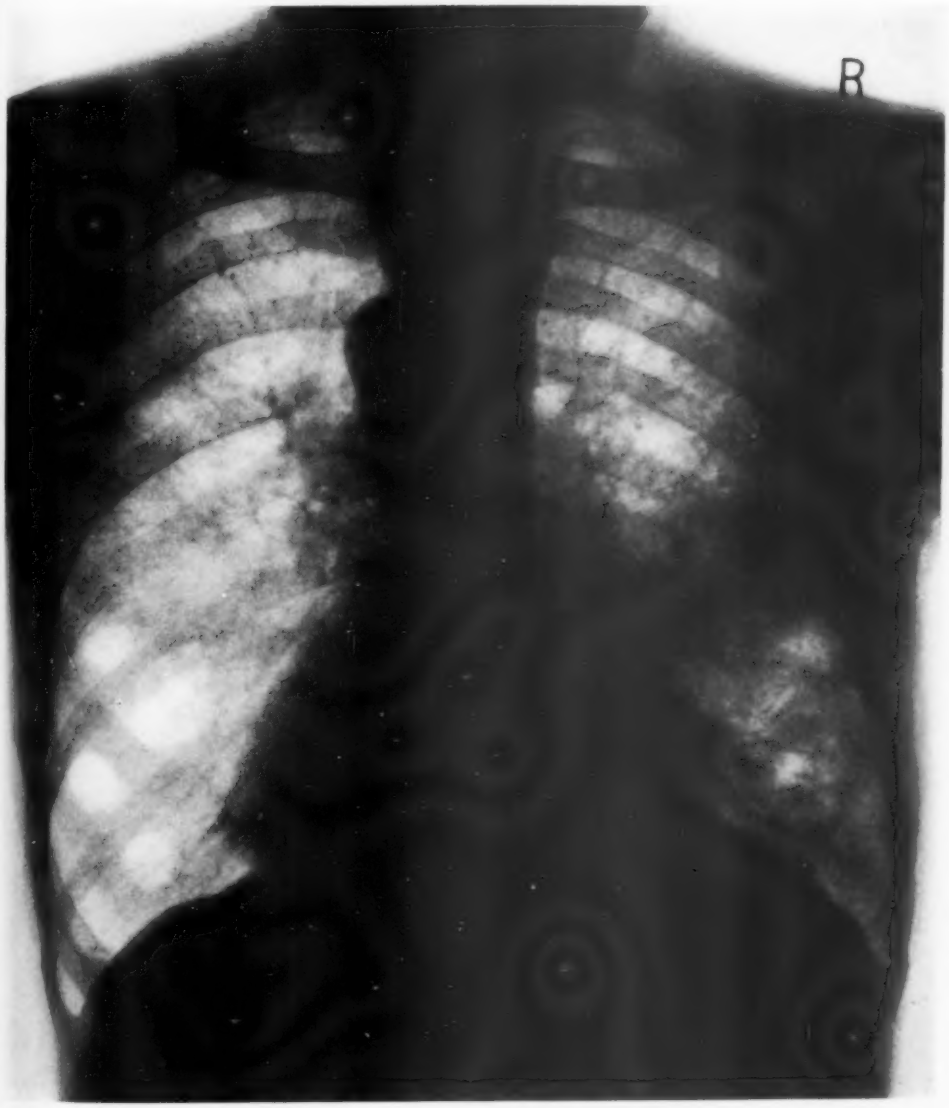


FIG. 3. *Case of J. B. Aleukemic lymphatic leukemia.* Chest plate taken on Nov. 14, 1935. Heavy infiltration of cells shown particularly in right lower lobe. Beginning infiltration in left side.

FIG. 4. *Case of J. B. Aleukemic lymphatic leukemia.* Chest plate taken on Nov. 29, 1935. Deep roentgen-ray therapy given on Nov. 16 resulted in some clearing of the involvement on the right side. However, the left side is now heavily infiltrated, particularly at the base.

cases, treated with roentgen-ray therapy with marked reduction in adenopathy, persist over long periods of time with low total counts and very little evidence of lymph node enlargement. Such cases are probably examples of aleukemic leukemia in which the proliferative forces have been reduced in activity. Other cases, with leukopenia developing after having shown previously high peripheral cell counts, may show marked evidences of infiltrative phenomena. These represent instances of aleukemic lymphatic leukemia in which loss of cells from the blood stream to the tissue spaces is particularly important. In this latter type it seems probable that the rate of production of the cells is not sufficiently high to balance the peripheral loss.

A consideration of these facts, therefore, suggests that, at times, in individual cases, any one of the three physiologic forces which are important in determining the peripheral level of cells may be the chief factor in the production of the so-called aleukemic state of lymphatic leukemia. The significance of analyzing each case from these standpoints for determining prognosis is obvious.

Discussion

From the observations made in the above cases, each cited as type specific for its class, it would seem that there are at least three mechanisms by which lymphoid tissue becomes hyperplastic: first, by excessive multiplication and maturation occurring simultaneously (e.g., infectious mononucleosis); second, by excessive multiplication with little or no concurrent maturation (e.g., the common types of lymphatic leukemia and pseudoleukemia); and third, by the metaplasia of cells with neoplastic alteration (e.g., lymphosarcoma). Each of these three basic pathologic states has been observed to occur in man. Cases of infectious mononucleosis with normal or nearly normal peripheral blood counts have been observed in our clinic (aleukocythemic infectious mononucleosis), whereas the lymphemia in other cases has been so marked as to make the differential diagnosis between lymphatic leukemia and infectious mononucleosis a matter largely dependent upon a careful qualitative study of the individual lymphatic cells. In these latter cases the determination of a continuance of normal maturation and the absence of amitotic division in the cells (inactive nuclei) have been among the important differential criteria. Important to this discussion is the fact that the phenomenon of cellular infiltration (marked anemia, thrombopenia, large liver, etc.) has never been observed in this disease because: 1, the cells are more mature and have correspondingly lowered potentialities for division; and 2, the cells continue to mature and hence tend to fulfill their life cycle, dying in large numbers. These factors discourage local growth tendencies in the tissue spaces where the cells may lodge, so that the phenomenon of infiltration (which largely represents in the last analysis local growth) is not seen in infectious states. In direct contrast with physiological lymphopoiesis as illustrated by infectious

mononucleosis, pathological lymphopoiesis is remarkable in that observed maturation of these cells is minimal in amount, whereas the evidence indicating profound propensities for division is an outstanding feature.

The evidence introduced in the body of this paper would seem to make it necessary, in order adequately to explain the phenomena observed, to hypothecate two distinct types of mechanisms responsible for the pathological lymphatic hyperplasias. On the one hand, cytologic and histologic evidence indicates that in one type of lymphatic hyperplasia, the mechanism is neoplastic (lymphosarcoma and leukosarcoma.) On the other hand the evidence secured by parallel methods of examination in the other group

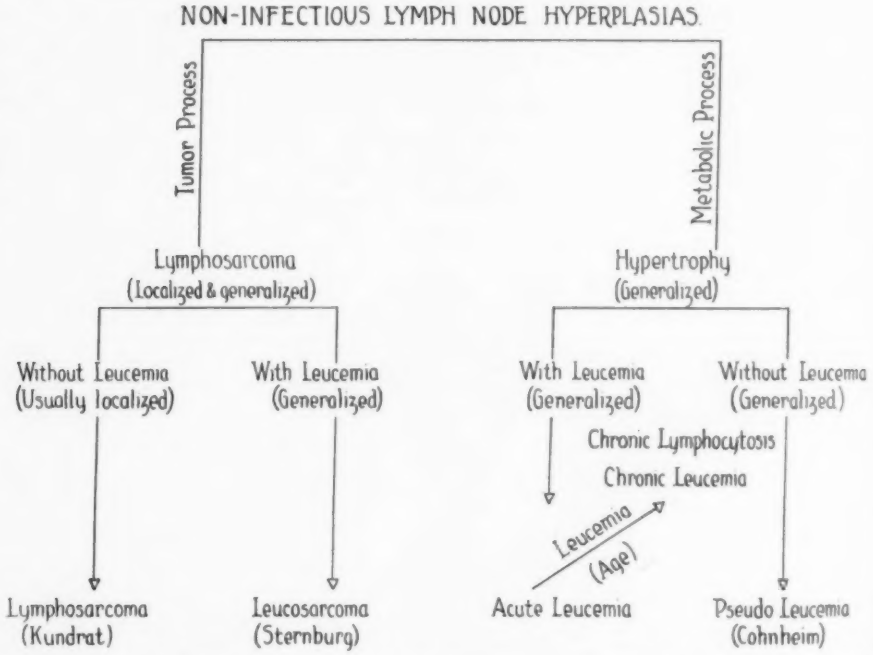


CHART 7. Graphic representation of the author's conception of the interrelationships existing between the primary non-infectious lymphocytic diseases. This scheme suggests that all of the lymphocytic hyperplasias of non-infectious origin consist essentially of two groups; that which is directly traceable to a neoplastic alteration in the reacting unit, the lymphocyte, and that group which is characterized by unlimited proliferation of lymphocytic elements resulting from an unknown but not a neoplastic mechanism. Either group may or may not exhibit leukemia.

(leukemia and pseudoleukemia) indicates that the mechanism is neither neoplastic in the same sense that lymphopoiesis is neoplastic in lymphosarcoma, nor essentially physiologic as in infectious states. In this latter (leukemic-pseudoleukemic) group the chief characteristic seems to be division without concomitant maturation, yet, withal, not neoplastic in character. The prototype of pernicious anemia immediately is recognized, and it is believed upon the basis of the evidence which we have secured that this type of lymphatic leukemia may be the result of a mechanism similar to

that which is responsible for the production of pernicious anemia. In order to account for the obviously neoplastic character of lymphosarcoma and leukosarcoma, it is necessary to postulate a second mechanism for the production of leukemia; that is, a neoplastic alteration in the lymphocytes which sometimes gain access to the blood stream (leukosarcoma). Lymphatic leukemia, according to this hypothesis which seems necessary to bring all the observed facts about this disease into accord, is the result of two vastly different etiologic agencies; the one neoplastic, the other possibly metabolic. The leukemias of the former type are usually more acute whereas those of the latter may be acute but usually are chronic. *The majority of the cases of chronic lymphatic leukemia are thus believed to be of metabolic origin.* Chart 7 illustrates the author's conceptions of the interrelationships of the various types of non-infectious lymphatic hyperplasias. Only those diseases which primarily affect the lymphocyte as such are shown.

It is emphasized that the conclusions as given above are not necessarily at variance with the well established data obtained from experimental leukemia in animals. The transmissability of tumors in mice [44, 45] and chickens,[46] which in some instances show lymphatic leukemia and in others lymphosarcoma without leukemia, is simply a repetition of the same phenomena observed in man under the lymphosarcoma-leukosarcoma sequence described by Sternberg in 1908. In the case of chickens, many of the so-called leukemic states are undoubtedly the response to infectious agents [47] and are therefore not true leukemias but rather lymphocytoses. Similar states in man, difficult to differentiate from true leukemias, are regularly observed [48] (see also discussion concerning infectious mononucleosis). It is not believed, however, that any of the true leukemias of man are the result of infectious agents for the various reasons given in previous chapters concerning the mechanism of the production of the cells in leukemia and their physical characteristics.

Conclusions

1. All theoretically predictable variations in lymphopoiesis probably occur in man. Each type may give rise to nearly the same clinico-pathologic syndrome, but essential differences can be determined and established by a study of the physical characteristics of the cells involved.

2. A study of cases showing pathologic lymphopoiesis points to the concept that there are probably two etiologic forces responsible for lymphatic leukemia in man which operate through two different mechanisms, the one neoplastic, the other metabolic.

3. Analysis of the question of idiopathic lymphatic hyperplasias indicates that there are only two fundamental types: (a) neoplastic alterations of the lymphocyte without leukemia (lymphosarcoma) and with leukemia (leukosarcoma), and (b) "benign" hypertrophies without leukemia (lymphatic pseudoleukemia) and with leukemia (some of the acute cases and probably most of the chronic lymphatic leukemias.)

4. Many acute leukemias are not true leukemic transformations of the underlying lymphatic tissues but are simply a vigorous cellular response to infectious agents conditioned by the host, the infectious agent, or both.

5. Aleukocythemic (aleukemic) leukemia may be the result of either type of mechanism which can produce lymphatic leukemia, but in all cases a low peripheral level of the lymphatic elements in the blood, when the stimulus to lymphopoiesis is strong, is the result either of a partially effective mechanism which normally is completely effective in preventing pathologic and immature cell-forms from leaving the mother tissues and entering the blood stream, or rapid migration of the pathologic cells from the blood into the tissue spaces.

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METABOLISM STUDIES IN MYASTHENIA GRAVIS BEFORE AND DURING THE ADMINISTRATION OF GLYCINE *

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SEVERAL attempts have been made to discover specific metabolic abnormalities in subjects with myasthenia gravis. The results in general have been contradictory and therefore inconclusive. The therapeutic value of glycine in this disease has caused a renewed interest in such studies, although the majority of the more recent investigations have dealt chiefly with the effect of glycine on the excretion of creatinine and creatine.

This investigation was undertaken, accordingly, to gain more complete information concerning the metabolism of patients with myasthenia gravis both before and during the administration of glycine. Complete studies in which the food, urine, and feces have been carefully collected and analyzed have been carried out on two subjects.

EXPERIMENTAL

Subject 1 was a woman, 40 years of age, who weighed 75.2 kg. and whose height was 5 feet and 8 inches (173 cm.). She had had myasthenia gravis for at least 10 years and for three years had been practically bedridden, until treatment with ephedrine was begun. Since that time she had been slowly improving, and at the time of this investigation she could get about fairly well with the aid of a wheel chair. She was still taking ephedrine—one 3/8 grain (0.025 gm.) capsule of ephedrine sulphate twice daily—when she came to the clinic, and this medication was continued throughout the study. The patient was placed on a constant diet containing 12.2 gm. nitrogen and about 1750 calories. The investigation consisted of a preliminary period of three days to allow the patient to come to equilibrium with the new diet, a control period of four days (I^1) † and a period of 11 days (II^1) on the diet plus 40 gm. glycine (7.40 gm. nitrogen) daily. At the end of this time the subject was unable to continue this regimen and the nitrogen of the diet was reduced to 10.7 gm. and the glycine to 20 gm. (3.70 gm. nitrogen) daily. After an interval of two days, collections of urine and stool were again resumed for a third period of 10 days (III^1).

Subject 2 was a man 24 years of age, who weighed 66.9 kg., and whose height was 5 feet and 8½ inches (174 cm.). Symptoms of myasthenia gravis first had been noted at the age of 15 years and had continued intermittently for about eight years. During the year before the patient's registration at the clinic, he had not been free of symptoms, and on admission he was extremely weak, had great difficulty in swallowing, and was confined to bed. For about one month he had been taking ephedrine sulphate, 3/8 to 3/4 grain (0.025 to 0.05 gm.) thrice daily. This medication was reduced to 3/8 grain (0.025 gm.) twice daily and was maintained at that level during our studies. This subject was placed on a constant diet containing 8.5 gm. nitrogen and about 1900 calories. After a control period of four days (I^2) there followed a period of 12 days (II^2) on the diet, plus 30 gm. glycine daily (5.56 gm. nitrogen). At the end of this period it became necessary to institute tube feeding, and the metabolic studies were, therefore, discontinued.

* Submitted for publication December 9, 1936. From the Mayo Clinic, Rochester, Minn.
† The significance of these symbols is evident in the table.

The complete output of urine was collected for each 24 hours and the nitrogen and sulphur partition products were usually determined immediately, although in a few instances it was necessary to use aliquot portions of mixed, two-day specimens. Aliquot portions of four to six consecutive specimens were acidified and mixed for the determination of the inorganic constituents. An exact duplicate of the 24 hour diet was ground and thoroughly mixed, dried in a current of air at about 70° C., and again ground and mixed to obtain samples suitable for analysis. Two separate 24 hour samples of food were prepared in this way for each of the different diets used. All uneaten food was collected, dried in a manner similar to that described and analyzed so that accurate corrections of the intake were possible. The feces were collected for periods of from four to six days and an enema of warm, distilled water was used to close each period. Hydrochloric acid was added to prevent loss of nitrogen and the specimens were prepared for analysis by drying in a current of warm air at 70° C. The following methods of analysis were used: total nitrogen, macro-Kjeldahl; urea, manometric determination of carbon dioxide after treatment with urease (Van Slyke [17]); ammonia, aeration and titration (Van Slyke and Cullen [18]); preformed creatinine (Folin [6]); total creatinine, the method of boiling with picric acid (Folin [6]); uric acid (Folin [8, 9]); total amino acid (Van Slyke [16] volumetric method, using an apparatus modified according to Koch [11]). For the determination of total sulphur in urine 1.0 c.c. was completely ashed with fuming nitric acid in an apparatus similar to that of Rossenbeck.[13] The ashed solution was evaporated to dryness with the addition of water and hydrochloric acid to remove the excess nitric acid. The dry residue was then taken up in 5 or 10 c.c. of 8.7 per cent trichloracetic acid and the sulphate present precipitated as the benzidine salt, essentially as described by Hubbard.[10] After centrifuging and washing, the benzidine sulphate was titrated with 0.01-normal sodium hydroxide. The inorganic fraction was similarly precipitated as benzidine sulphate from urine appropriately diluted with trichloracetic acid. Hydrolysis of conjugated sulphates was accomplished by heating the trichloracetic acid dilutions in calibrated tubes for 15 minutes in boiling water. The trichloracetic acid lost by decomposition was replaced by the addition of a predetermined quantity of 40 per cent solution, the mixture made to a definite volume, and the sulphate present, inorganic plus conjugated, was precipitated and titrated as the benzidine salt. From these determinations the neutral sulphur and conjugated sulphate fractions were found by calculation. For the determination of total sulphur in food and feces suitable samples were burned in an oxygen bomb according to Berthelot as described by Sherman,[14] after which the sulphate in the bomb washings was precipitated and weighed as barium sulphate.

The inorganic constituents of urine, food and feces were determined on hydrochloric acid extracts of samples which had been ashed in platinum in an electric muffle at 450° C. The colorimetric method of Fiske and Subbarow [5] was used for the determination of phosphate. In the case of urine the inorganic phosphorus as determined in unashed samples agreed with the determinations on the ashed samples within 1 or 2 per cent. Calcium and potassium were determined according to Tisdall and Kramer.[15] Magnesium was precipitated as magnesium ammonium phosphate according to Tisdall and Kramer, after which the phosphate in the precipitate was determined by Fiske and Subbarow's method. Butler and Tuthill's [4] adaptation of the zinc uranium acetate method of Barber and Kolthoff [3] was used for the determination of sodium.

Results

The results of the balance studies are summarized in table 1 in terms of the average daily balances for the control periods and the periods during which glycine was administered. In period I [1] for subject 1 the balances

TABLE I

Balance Studies in Myasthenia Gravis

Constituent	Subject 1 *				Subject 2 †			
	Period I [1] four days; no glycine		Period II [1] eleven days; 40 gm. glycine daily = 7.40 gm. nitrogen		Period I [2] four days; no glycine		Period II [2] twelve days; 30 gm. glycine daily = 5.56 gm. nitrogen	
	Daily intake, gm.	Daily balance, gm.	Daily intake, gm.	Daily balance, gm.	Daily intake, gm.	Daily balance, gm.	Daily intake, gm.	Daily balance, gm.
Nitrogen	12.20	−0.02	19.60	−0.03	8.20	−3.91	13.52	−3.11
Sulphur	0.89	+0.04	0.89	+0.01	0.70	−0.16	0.69	−0.14
Phosphorus	1.25	+0.08	1.25	+0.05	1.13	−0.26	1.10	−0.21
Sodium	3.38	+1.33	3.38	+0.49	2.44	+0.20	2.45	+0.23
Potassium	2.52	−0.49	2.52	−0.19	2.98	+0.02	2.88	−0.08
Magnesium	0.20	−0.02	0.20	−0.01	0.19	−0.02	0.21	−0.01
Calcium	1.07	+0.15	1.07	+0.17	0.86	−0.19	0.83	−0.20

* Three-fourths grain (0.05 gm.) ephedrine sulphate daily. Course of disease: condition stationary; slight but insignificant loss in weight.

† Three-fourths grain (0.05 gm.) ephedrine sulphate daily. Course of disease: condition progressively getting worse with marked loss of weight—3 kg.

for nitrogen, sulphur, phosphorus, magnesium, and calcium were close to equilibrium. Likewise during period II,[1] when glycine was administered, there was remarkably little change in these balances. In a subsequent period, not shown in table 1, during which time the intake of food and glycine was reduced, the balances continued to be much like those observed for period II.[1] Apparently there was a large retention of sodium in period I [1] but this may be ascribed to the fact that the supplementary sodium chloride of the diet was not sufficiently accurately weighed during this period. The retention of sodium in period II [1] was 0.49 gm. per day, a value not abnormally high in view of the fact that no correction for loss of sodium through the skin could be made. The potassium balance in period I [1] appeared to be significantly negative. In period II [1] this balance became somewhat less negative.

In contrast to subject 1, subject 2 was, during the control period, in definite negative balance as regards nitrogen, sulphur, phosphorus, and calcium, but in approximate balance as regards potassium, magnesium, and possibly sodium. During the administration of glycine, period II,[2] the loss of nitrogen decreased but the balance was still highly negative. No marked changes occurred in the balances of the other constituents.

The data concerning the nitrogen partition products in the urine are summarized in table 2 in terms of the average daily values. For the purpose of showing in greater detail the changes in distribution during the periods of administration of glycine, the results of the daily determinations

TABLE II

Nitrogen Partition Products in the Urine before and during the Administration

TABLE II

Nitrogen Partition Products in the Urine before and during the Administration of Glycine

Period	Days	Glycine nitrogen, gm.	Food nitrogen, gm.	Total nitrogen		Urea nitrogen		Ammonia nitrogen			Preformed creatinine nitrogen		Creatine nitrogen			Uric acid nitrogen			Total amino acid nitrogen		
				Daily, gm.	Increase, per cent of glycine nitrogen	Daily, gm.	Per cent of total nitrogen	Daily, gm.	Per cent of total nitrogen	Change, per cent	Daily, gm.	Per cent of total nitrogen	Daily, gm.	Per cent of total nitrogen	Change, per cent	Daily, gm.	Per cent of total nitrogen	Change, per cent	Daily, gm.	Per cent of total nitrogen	Change, per cent
Subject 1																					
I[1]	4	0	12.20	11.54		9.86	85	0.41	3.6		0.43	3.5	0.17	1.5		0.18	1.6		0.17	1.5	
II[1]a	1	7.40	12.20	16.58	68	13.98	84	0.41	2.5	0	0.40	2.0	0.24	1.4	+ 41	0.24	1.4	+33	0.59	3.6	247
b	6	7.40	12.20	19.70	110	17.29	88	0.62	3.1	+ 51	0.44	2.2	0.25	1.3	+ 47	0.22	1.1	+22	0.41	2.2	141
c	4	7.40	12.20	18.61	96	16.89	91	0.60	3.2	+ 46	0.45	2.3	0.25	1.3	+ 47	0.19	1.0	+ 5.6	0.38	2.0	124
Average, II[1]	11	7.40	12.20	19.02	101	16.84	89	0.60	3.2	+ 46	0.44	2.2	0.25	1.3	+ 47	0.21	1.1	+17	0.41	2.2	141
Subject 2																					
I[2]	4	0	8.20	11.55		9.55	83	0.49	4.2		0.55	6.8	0.04	0.78		0.15	1.3		0.21	1.8	
II[2]a	3	5.56	8.29	16.10	82	11.44	71	3.29	20.4	+571	0.53	3.1	0.13	0.81	+ 44	0.19	1.2	+27	0.40	2.5	90
b	3	5.56	8.29	16.08	81	12.34	77	2.23	13.8	+355	0.54	3.2	0.21	1.30	+133	0.17	1.1	+13.3	0.36	2.2	71
c	6	5.56	7.62	16.04	81	12.88	80	0.95	5.9	+ 94	0.53	4.0	0.18	1.12	+100	0.17	1.1	+13.3	0.37	2.3	76
Average, II[2]	12	5.56	7.96	16.07	81	12.39	77	1.86	11.5	+281	0.54	4.1	0.17	1.06	+ 89	0.17	1.1	+13.3	0.37	2.3	76

Subject 1. Increased excretion of nitrogen = 101 per cent of increased intake of nitrogen.
Sum of increase in urea, ammonia, creatine, uric acid, amino acid = 101 per cent of increased intake of nitrogen.

Subject 2. Increased excretion of nitrogen = 81 per cent of increased intake of nitrogen.
Sum of increase in urea, ammonia, creatine, uric acid, amino acid = 80 per cent of increased intake of nitrogen.

have been grouped arbitrarily into three subperiods during each of which the daily values remained relatively constant.

The nitrogen distribution during the control periods was apparently normal for each subject, except for the presence of some creatine, a condition occasionally encountered in myasthenia gravis.[1] During the periods of administration of glycine there occurred in subject 1 a marked temporary retention of nitrogen for the first day or two. This was later excreted, however, and the average increase in the urinary nitrogen for the entire period was equivalent to 101 per cent of the nitrogen ingested as glycine. For subject 2, the increase in the nitrogen of the urine was equivalent to only 81 per cent of the glycine ingested.

The increased urinary nitrogen was largely in the form of urea. Changes in the other nitrogenous constituents were relatively small and accordingly the nitrogen partition products remained essentially normal. For subject 1, the average change in urea accounted for 93 per cent of the increased nitrogen, and that of ammonia for 2.6 per cent. In the urine specimens of subject 2 the urea appeared to be markedly unstable,* and the change in urea accounted for only 63 per cent of the increased nitrogen, while the ammonia was unusually high and accounted for an average of 30 per cent of the increased nitrogen. Thus, for both subject 1 and subject 2, the changes in urea plus ammonia accounted for substantially the same fraction of the increased nitrogen in the period when glycine was being given.

The excretion of creatinine during the periods of administration of glycine was unchanged as compared with the excretion during the control periods. Creatine, however, was excreted in definitely increased quantities. This response to glycine we have considered in detail in previous publications.[1, 2] A slight increase in the excretion of uric acid by both subjects was observed. This was characterized by an initial increase followed by a gradual return to approximately the levels of the control periods. A marked increase occurred in the excretion of total amino acids by both subjects. Analyses for amino acids by Folin's [7] method indicated that the free amino acids accounted for only about 40 per cent of this increase. It was found later, however, that the permutit sample used in these determinations absorbed both ammonia and amino acids, and subsequent analyses by the method of Van Slyke have shown that practically all of the increase in excretion of amino acid during the administration of glycine is in the free amino acid fraction. Relative to the amounts of glycine involved, the increases were small, only about 3 per cent of that ingested.

The increased excretion of urea, ammonia, creatine, uric acid and amino acids in the periods of administration of glycine accounted satisfactorily for all of the extra nitrogen appearing in the urine, 100 per cent and 99 per cent for subjects 1 and 2, respectively. The average undetermined nitrogen fractions, therefore, were not appreciably altered by glycine, and

* We have encountered this same type of instability in the urine of several other subjects who were taking glycine.

TABLE III

Sulphur Partition Products and Inorganic Phosphate Excretion in the Urine before and during the Administration of Glycine

Period	Days	Glycine nitrogen	Total sulphur			Neutral sulphur			Conjugated sulphur			Inorganic sulphur			Inorganic phosphate	
			Intake	Daily, gm.	Change, per cent	Daily, gm.	Change, per cent	Per cent of total sulphur	Daily, gm.	Change, per cent	Per cent of total sulphur	Daily, gm.	Change, per cent	Per cent of total sulphur	Daily, gm.	Change, per cent
Subject 1																
I[1]	4	0	0.891	0.770		0.102		13.2	0.054		7.0	0.615		79.9	0.81	
II[1]a	1	7.40	0.891	0.740		0.096	− 5.9	13.0	0.066	+ 22.2	8.9	0.579	− 5.9	78.2	1.02	+25.9
b	6	7.40	0.891	0.851	− 3.9	0.127	+25.5	14.9	0.054	0.0	6.3	0.670	+ 8.9	78.9	0.86	+ 6.2
c	4	7.40	0.891	0.793	+10.5	0.141	+38.2	17.8	0.047	− 13.0	5.9	0.606	− 1.5	76.4	0.84	+ 3.7
Average, II[1]	11	7.40	0.891	0.820	+ 3.0	0.129	+26.5	15.7	0.053	− 1.9	6.5	0.638	+ 3.7	78.0	0.86	+ 6.2
Subject 2																
I[2]	4	0	0.695	0.806		0.097		12.0	0.016		2.0	0.693		86.0	1.01	
II[2]a	3	5.56	0.705	0.807	+ 0.1	0.130	+34	16.0	0.032	+120	4.0	0.646	− 6.8	80.0	0.98	− 3.0
b	3	5.56	0.705	0.766	− 5.0	0.103	+ 6	13.4	0.040	+150	5.2	0.624	−10.0	81.5	0.93	− 7.9
c	6	5.56	0.664	0.757	− 6.1	0.122	+26	16.1	0.047	+194	6.2	0.587	−15.3	77.5	0.90	−10.0
Average, II[2]	12	5.56	0.685	0.772	− 4.3	0.119	+22	15.4	0.042	+165	5.4	0.611	−11.8	79.1	0.93	− 7.9

it appears that no very large amounts of unknown nitrogen-containing substances were formed, although the possibility of alterations in the character of the undetermined nitrogen fraction cannot be excluded.

In table 3 the data for the sulphur partition products of the urine, and for the excretion of inorganic phosphate, are presented in a form similar to that employed in table 2. The excretion of total sulphur and inorganic sulphate by subject 1 during administration of glycine was roughly parallel to the excretion of nitrogen, while there was no change in the conjugated sulphate fraction. There was a small decrease in the excretion of total sulphur by subject 2, with a more marked decrease in the inorganic fraction. At the same time the conjugated sulphates increased considerably over the rather unusually low value of the control period. There were rather substantial increases in the excretion of neutral sulphur by both subjects. The excretion of phosphate by subject 1 was markedly increased on the first day of administration of glycine, but later returned to a level only slightly above that of the control period. On the other hand, the excretion of phosphate in the urine by subject 2 progressively decreased during the period of administration of glycine.

Comment

On the basis of these results it seems impossible to conclude that there is any particular metabolic abnormality in myasthenia gravis. The two subjects presented certain marked differences, particularly in respect to the balance studies. These may be ascribed to their widely different clinical conditions, and it may be suggested that the results of previous attempts to demonstrate metabolic abnormalities probably have been determined largely by the condition of the patient when studied. The tendency toward a negative potassium balance observed in subject 1 may possibly have some significance, in view of the recent reports of Laurent and Walther [12] that large doses of potassium salts afford temporary relief in this disease.

The response of the two subjects to administration of glycine, as shown by the nitrogen and sulphur partition products in the urine, was, on the whole, quite similar. Aside from the increased excretion of urea, ammonia, and amino acids there were small but definite changes in the excretion of creatine, uric acid, and neutral sulphur. This suggests that glycine exerts some influence on the so-called " endogenous " metabolism. On the other hand, the changes appeared at variable times after the beginning of administration of glycine, and did not run parallel courses throughout the experiments, so that it seems useless to attempt interpretations until many more data have been accumulated.

Summary

In complete balance studies of two subjects who had myasthenia gravis, during which the nitrogen and sulphur partition products of the urine were also determined, it was not possible to demonstrate any metabolic abnormality which could be considered characteristic of the disease.

The type of balance obtained appeared to depend largely on the condition of the subject. One subject was in approximate equilibrium as regards the nitrogen, sulphur and inorganic constituents. The administration of glycine to this individual had remarkably little influence on the various balances. The second subject was in markedly negative nitrogen balance throughout the experiments although, during the administration of glycine, the large net loss of nitrogen was somewhat decreased. Glycine exerted little influence on the balance of the other constituents.

The extra nitrogen appearing in the urine during the administration of glycine was chiefly in the form of urea and ammonia. The urinary excretion of creatine, uric acid, amino acids, and neutral sulphur was also slightly but definitely increased.

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THE TREATMENT OF ADDISON'S DISEASE WITH SODIUM COMPOUNDS, WITH THE REPORT OF ONE CASE AND THE SUMMARIES OF ELEVEN OTHER COLLECTED CASES THUS TREATED *

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The treatment of Addison's disease has undergone a marked change in the last five years. Ever since 1855, when Addison first described the insufficiency disease of the suprarenal cortex that now bears his name, investigators have been trying to devise an adequate treatment for this condition.

Muirhead Régime

Previous to 1930, physicians relied chiefly on the Muirhead régime,[1] which consisted of administering epinephrine by mouth, by rectum, and subcutaneously at frequent intervals and up to the patient's tolerance, together with "desiccated cortex" by mouth, 10 to 15 grains daily. Results from this regimen were observed in 10 to 20 per cent of the cases.

Cortical Hormone Therapy

In 1930 Swingle and Pfiffner [2] announced a potent extract of the adrenal cortex, and with Hartman [3] and others developed the cortical hormone substitution therapy. This treatment has been of considerable value in meeting the critical episodes of the disease, and in restoring many invalids to a reasonable degree of health. Snell,[4] however, in reporting 46 cases treated with the extract, pointed out that the patients have not been restored to full efficiency and their lives have not been indefinitely prolonged; consequently the therapy can not be considered entirely satisfactory. In addition, the cost of the cortical extract makes this form of treatment prohibitive at present.

Sodium Compound Therapy

Recently sodium compounds have been found to have a definite place in the treatment of Addison's disease. G. N. Stewart [5] in 1924 paved the way for this discovery by explaining the cause of previous discrepancies in the results of experimental adrenalectomy, as due to such factors as shock resulting from poor quality surgery, the nature and duration of the anesthesia, undue loss of heat, and lack of attention to the nutritive state of the animals before and after the operations. He found that the operations had

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not been performed in such a way as to insure complete removal of the glands, and in almost all instances the extirpation had not been controlled by adequate postmortem search for remaining adrenal tissue or accessory gland substance. Stewart pointed out that animals surviving only a few days after adrenalectomy cannot rightfully be assumed to be suffering from adrenal insufficiency.

Following such caustic criticism, investigators began to control their work more carefully, and results appeared which could be confirmed at other hands. Stewart himself, with Rogoff,[6] was able to keep dogs alive for sufficient periods to rule out the question of shock, and among other observations noted that the use of Ringer's solution with dextrose intravenously, in seven out of 36 bilaterally adrenalectomized dogs, increased the span of life considerably and ameliorated the symptoms. In 1926 Banting and Gairns [7] from their experience with 56 dogs found that saline increased the length of life. Lucas [8] noted a fall in the chlorides of the blood in bilaterally suprarenalectomized dogs. In 1927 Corey [9] reported that oral administration of large quantities of fluid to bilaterally adrenalectomized cats prolonged life, and that solutions of certain substances, notably glucose and sodium chloride, were more effective. Zwemer [10] also found an amelioration of symptoms with administration of fluid following bilateral adrenalectomy. All of these investigators failed to realize the significance of the sodium ion.

The first significant step in the discovery of the value of sodium salts seems to have been taken by Baumann and Kurland [11] in 1927. Their adrenalectomized cats lived five to six days; consequently, they were able to compare the blood chemistry of such animals with a normal unoperated group. In the adrenalectomized animals the sodium of the blood plasma fell from a normal of 375 milli-equivalents per liter to 320, or a loss of 15 per cent; while the chlorides fell from 415 to 378, or a loss of 9 per cent. At the same time there was an increase of 42 per cent in the potassium of the plasma.

Marine and Baumann [12] studied the effect of various solutions on the length of life of bilaterally adrenalectomized cats. Their series included 167 cats, of which 101 were considered sufficiently free from possible complicating factors to be included in tables of analysis. They found that the animals would live five days without any medication; 10 days if cortical extracts were injected; and 15 days if a daily injection of 50 c.c. of normal saline was given intraperitoneally. Concentrated saline shortened the period of life, and hence it was assumed that water to bring the saline to a physiological solution was necessary. However, diuretic solutions, such as isotonic glucose, failed to prolong life materially, and therefore the value of the treatment could not be attributed to the fluid alone. Ringer's solution, physiological saline, sodium acetate, and sodium glycero-phosphate were found to have about the same effect, and consequently it appeared that the sodium and not the chloride is important. They felt their evidence indicated a specificity in the action of the sodium ion.

The next and most important step was taken by R. F. Loeb [13] who made a complete analysis of the inorganic bases of the blood plasma of patients with severe Addison's disease. The normal level of sodium in the blood plasma he assumed to be about 138 milli-equivalents per liter (317.4 mg. per cent), which corresponds well with the figure of 140 milli-equivalents given by Butler and Tuthill.[14] Loeb found the chief abnormality in his patients to be in the sodium content, which in three cases was respectively 109, 131, and 108 milli-equivalents per liter (250, 301 and 248 mg. per cent), a definite decrease in each instance. The potassium content was very high, in two cases being 8.7 and 7.1 milli-equivalents per liter (34 and 27.7 mg. per cent), the normal being 4.8 (18.7 mg. per cent); the chlorides being reduced to 70 and 73 (248 and 259 mg. per cent), the normal being 103 [15] (365.6 mg. per cent).

Working with Atchley, Benedict, and Leland, Loeb then made studies of the inorganic base balance in three dogs before and after adrenalectomy.[16] The removal of only one adrenal gland produced no change in any of the dogs, but the removal of the remaining gland caused a decrease in the sodium of the blood-serum from 147 to 126 milli-equivalents per liter; while the potassium level was slightly elevated. At the same time the sodium in the urine increased markedly, and the chlorides were increased also, but not to the same extent as the sodium.

These observations were confirmed by Harrop, Soffer, Ellsworth, and Trescher.[17] They produced bilateral adrenalectomy in dogs, and then maintained them in a state of normal health with cortical extract until the animals had fully recovered from the effects of the operation. Upon ceasing the extract, the dogs had a characteristic alteration in the blood and urinary findings: the plasma concentration increased; the sodium concentration in the plasma decreased, and with it the chlorides and part of the body water; while the potassium and magnesium were increased. At the same time within 48 to 72 hours the sodium, chloride, and water excretion in the urine was much increased. When the extract was resumed, there was retention of sodium, and with it chloride and water in the body in excess of the excretion. This continued until the animals returned to normal. In another series of dogs, the extract was continued, and the animals fed a salt-poor diet, following which insufficiency appeared. The dogs were returned to a normal state by injections of salt alone. These same animals were then placed on the identical salt-poor diet, with 1.5 grams of salt added, and no evidence of insufficiency appeared. From this, these investigators suggested that the dosage of the cortical extract may be reduced to a fraction of its original amount by using a high salt diet with it.

The proof of the connection between sodium and dysfunction of the adrenal cortex was finally established by Loeb,[18] who gave a patient salt and found marked improvement. The patient, a woman, on admission had a classical picture: progressive weakness, loss of appetite and weight, increasing pigmentation of skin, nipples, and buccal membranes, mild sec-

ondary anemia and a blood pressure of 90 systolic and 60 diastolic. At that time the sodium concentration of her blood was 123 milli-equivalents per liter (284 mg. per cent); normal being 138 (317.4 mg. per cent). One week later the sodium had fallen to 107 (247.9 mg. per cent), and the woman was in a much more severe condition, with profound exhaustion, slight dyspnea, increasing nausea, and recurrent vomiting. The chlorides had decreased proportionally; the potassium had risen and the blood pressure was 65 systolic and 48 diastolic. She was given 9.5 grams of sodium chloride daily by proctoclysis, and 5 grams a day by mouth in capsules. Within four days the clinical improvement was so striking that rectal administration was stopped, and the convalescence maintained with five to seven grams of salt a day in addition to a liberal amount in the diet. She continued to gain, and was discharged on a regular diet plus one and a half teaspoonfuls of salt daily.

She remained well for five months, gained seven pounds, and was able to do her housework. Her sodium level was then entirely normal. At this stage she developed some edema under the eyes, and was advised to take a low salt diet, containing about 2 grams of sodium chloride. Two days later she was so weak she had to go to bed, and for the next five days became progressively weaker and vomited at frequent intervals. She was readmitted to the hospital and was found to have a low serum sodium reading of 126 milli-equivalents (291.6 mg. per cent), with a low chloride and a high potassium level. She was immediately given seven grams of sodium chloride by mouth, and a rectal drip of 200 c.c. of physiological saline every four hours. No other treatment was used. Within three days she had improved to such a remarkable extent that the rectal instillations were stopped, and she was discharged on the eighth day in excellent health, having gained four pounds. Her blood chemistry was again entirely normal. Subsequently Loeb [19] reported that more than two years after the first admission the same patient continued to maintain her improvement, and complained only of usually feeling cold and of tiring rather easily. On her own initiative she had increased the sodium chloride to 15 grams daily. The blood sodium level and the blood pressure were still normal, with the pigmentation slightly decreased.

Loeb, Atchley, Gutman, and Jillson [20] have repeated this experiment on another patient. She was at first allowed to eat an ordinary diet with as much salt as she wanted. On this she was able to be up in the ward, although she complained of nausea, occasional abdominal pain, and slowly increasing weakness. She was then put on a low salt diet, and immediately became worse; with dizziness, nausea, and marked prostration, so that at the end of the first day she had to stay in bed. The sodium level in the serum, which had been falling gradually during the normal diet, took a decided drop after 48 hours on the low salt diet. The addition of excess salt to the diet led to rapid recovery, and the patient was able to get up in

two days, and leave the hospital in five, when the sodium had risen again to normal. She was instructed to continue oral salt in addition to a highly seasoned diet.

These observations have been confirmed by Harrop, Weinstein, Soffer, and Trescher.[21] They found that with a high salt diet they could diminish the potency of the cortical extract to such an extent that it would not have any effect in prolonging the lives of adrenalectomized dogs, and yet the patients remained symptomless, and continued to gain weight and strength on it for nine months. However, when the extract was replaced with a 'hypo' of sterile water in one patient, there was a relapse after six weeks. The patient improved again when put back on the low potency extract and the high salt diet. The authors then placed the patient on a low salt diet, while continuing the extract, and within two days the patient lost appetite and complained of great weakness. The sodium and the chloride levels in the blood serum were considerably lowered. When treated with intravenous saline the patient gradually improved, and 22 days after the start of the experiment, the blood findings were again essentially normal. The same workers had similar results in another case, with a definitely low sodium level, which was restored to normal after one week on a high salt diet and oral salt. The authors then removed the extract entirely from four patients, and placed them on a highly seasoned diet with additional salt. All continued to feel strong, were found to tire less easily, and were relieved of the persistent recurring nausea and vomiting that had been present before treatment. There was a definite gain in weight in one patient.

In January 1934, Sears [22] in England studied a case of Addison's disease of seven years' duration. He found the blood sodium level to be very low on admission. After one week on a regular diet and sodium chloride by mouth daily, the sodium level had risen to well above normal, and there was marked subjective improvement. The patient was discharged on a maintenance dosage of salt. Shortly after, Snell [23] at the Mayo Clinic reported a case of Addison's disease of exceptionally long duration (17 years). The extended course of the disease seemed to be partially attributable to the fact that the patient of his own accord had been using salt excessively for the past few years. The patient had an acute episode in May 1934, and was treated with cortical extract and sodium chloride daily with marked clinical improvement but no change in the electrolytes of the blood. Howell [24] in England in May 1934 found the blood sodium level in a case of Addison's disease of six months' duration to be only slightly decreased on admission. He placed the patient on sodium chloride and reported a dramatic effect in 24 hours, with the patient changed from a listless, apathetic invalid to an alert individual sitting up in bed, reading. When the salt dosage was cut in half without the patient's knowledge, anorexia, weakness and vomiting occurred within one week. The patient was restored to normal by returning to the original dosage.

The Salt-Poor Diet Confirmatory Test for Addison's Disease

Harrop, Weinstein, Soffer, and Trescher [21] suggested that the withdrawal of salt from the diet should be used to confirm the presence of Addison's disease. They recommended that this test should be used only if large amounts of potent cortical extract are available, as the condition of the patient may be very alarming after 24 to 48 hours on a low salt diet. If, however, the patient is no worse for the deprivation of salt, it must be considered extremely unlikely that he has Addison's disease.

Nettrour and Rynearson [25] at the Mayo Clinic made use of this test in the case of a 21 year old boy with a typical history of nausea, vomiting, and extreme weakness and fatigue, but without the characteristic pigmentation. On admission the blood pressure was 78 systolic and 52 diastolic while reclining; the sodium and chloride levels were considerably decreased; the basal metabolic rate was subnormal, and there was a mild secondary anemia. The patient was placed on a salt-poor diet for five days, with a marked increase in the severity of the nausea, vomiting and prostration, while the chloride fell to a very low level. Intravenous physiologic saline, cortical extract, and sodium chloride by mouth daily restored the patient to normal in four days, the blood electrolytes returning to approximately normal level. The therapeutic test of the salt-poor diet as an aid in the diagnosis of Addison's disease was therefore entirely successful.

Touw and Noordhoek Hegt [26] in Holland observed clinical manifestations and blood chemistry of two patients with Addison's disease during periods of normal, salt-poor, and excessive salt diets. There was a noteworthy parallelism between the clinical improvement of the patients and the rise of the sodium content of the blood after the oral administration of 20 to 35 grams of sodium chloride daily.

Loeb [19b] recently reported a case clearly demonstrating the serious consequences that may follow the salt-poor diet test. His patient after four days of salt deprivation suddenly developed shock, although only a relatively small decrease of the sodium level was present, and then continued in an alarming state in spite of large amounts of cortin, fluid and salt. Hypoglycemia, ketosis, and dehydration were found to be complicating the picture, and were combated for a week with a continuous infusion of salt and dextrose before the patient was considered out of danger. Loeb says significantly, "It is unfortunate that a diagnostic procedure so highly specific as is salt withdrawal in Addison's disease should be attended by such grave consequences to the patient."

Anterior Lobe Pituitary Extract Therapy

Wilder [27] at the Mayo Clinic in November 1934 reported two cases of Addison's disease treated with cortical extract, sodium chloride by mouth, and anterior lobe pituitary extract. He pointed out that the majority of the patients with Addison's disease required a larger than normal supply

of sodium chloride even when receiving adequate amounts of cortical extract, and suggested a secondary deficiency in the hormone of the anterior lobe of the pituitary body because of changes in the basophile and chromophile cells of that gland found in cases of Addison's disease.[28] He showed, as had previous workers, that the patients could be restored to approximately normal health with cortical extract and oral sodium salts, and that relapses occurred when either of these forms of medication was discontinued. He found, however, that when anterior lobe pituitary extract was given in addition to the cortical extract and the salt, the patients felt stronger and were considerably less sensitive to the deprivation of the sodium chloride. Wilder suggested that this sensitiveness may be due to secondary insufficiency of the anterior lobe of the pituitary associated with the adrenal insufficiency in Addison's disease.

The Specificity of the Sodium Ion

It was pointed out by Loeb and his associates [20] that there is apparently a specific relation between the sodium ion and the adrenal glands. He suggested that these organs play an important rôle in the regulation of the sodium metabolism in the normal body, analogous to that of the parathyroid with calcium and phosphorus, and that the sodium depletion occurring in adrenal insufficiency is dependent therefore on a disturbance of this normal function. There is loss of sodium without a change in potassium excretion, whereas in other clinical states with base loss the sodium depletion is accompanied by a parallel loss of potassium; as in starvation,[29] diabetes,[30] ammonium chloride acidosis,[31] and severe diabetic glycosuria.[30] Zwemer [32] in 1934 reviewed the experimental data and similarly concluded that the adrenal cortex has a regulative effect on the salt and water metabolism of the cell.

The experimental evidence of the specificity of the sodium ion in adrenal cortex insufficiency can be found in the work of Marine and Baumann [12] already cited. They showed that the various isotonic fluids that were effective in prolonging the life of bilaterally adrenalectomized cats contained only the sodium ion in common, and that isotonic solutions such as glucose failed to prolong life materially.

Clinically this point was clearly demonstrated in the case reported in March 1935 by Blankenhorn and Hayman.[33] They treated a case of Addison's disease of three months' duration with oral sodium chloride daily, and obtained subjective and clinical improvement. The blood sodium content and the blood pressure rose from low levels to approximately normal. The provocative salt-poor diet test readily confirmed the diagnosis. When the salt medication was discontinued the patient promptly had a relapse with weakness, anorexia, nausea and irrationality, and the blood chlorides again fell to a low level. The patient failed to respond to cortical extract intramuscularly and intravenously, and it was only by giving saline intra-

venously that he was saved from imminent disaster. The patient was then returned to oral salt daily, and remained in good health for several weeks. At that point it was decided to test the specificity of the sodium ion. Accordingly the sodium chloride was replaced by other chloride salts. In three days the patient developed abdominal pain, nausea, and vomiting. Intravenous saline and oral sodium chloride then restored the patient to normal, and after two weeks the patient was in excellent health. A mixture of sodium salts, the sulphate, the phosphate, and the bicarbonate, containing an amount of sodium equal to that previously given, was then substituted. This was given for 17 days without any discomfort, with the patient continuing apparently well. The specificity of the sodium ion was thus clearly demonstrated. The patient was put back again on sodium chloride medication, and after two weeks, in spite of 16 grams daily, developed a severe crisis complicated by bronchopneumonia and expired.

We obtained similar results with the case herein reported. After demonstrating the improvement of the patient on sodium chloride and, after confirming the diagnosis with the salt-poor diet test, we restored the patient to normal by oral sodium chloride and then placed him on a mixture of sodium biphosphate and sodium bicarbonate. This sufficed to maintain excellent health, according to all tests, for over two weeks, again demonstrating the specificity of the sodium ion.

The Prolongation of Life

The question of how much prolongation of life can be expected from these therapeutic advances naturally arises. Experimental adrenalectomized animals apparently can be kept alive almost indefinitely with injections of potent cortical extract. The effect of sodium salts alone on adrenalectomized animals has been studied by several investigators.

Rubin and Krick [34] found that untreated bilaterally operated rats could not be kept alive over 10 days, but if, while exhibiting symptoms of severe insufficiency, they were given a special solution of calcium, magnesium, sodium and potassium chlorides, they could be restored to normal in four to five hours, and could be kept alive over four months. Gaunt, Tobin and Gaunt [35] in October 1934 studied another series of bilaterally adrenalectomized rats. Only four of the adult control series of 24 survived over 30 days. The experimental series of 23 rats was given a sodium chloride solution for 30 days following the operation. Five animals succumbed 14 to 25 days after operation with typical symptoms of adrenal insufficiency; six animals survived the treatment period and were in good health, but when returned to normal diet and distilled water, developed adrenal insufficiency and died in 10 to 15 days; 12 animals, approximately 50 per cent, survived in good health and remained well afterwards on normal diet and distilled water. When killed and autopsied eight or more weeks later, seven of these were found to have accessory glands.

Swingle, Pfiffner, Vars, and Parkins [36] fed sodium chloride to the point of tolerance to seven bilaterally adrenalectomized dogs while withholding cortical extract. Three animals remained free from symptoms for 14 days, one for 12 days, one 21 days, one 19 days, and one 50 days. Salt was withdrawn from the diet of the long surviving animal on the fiftieth day, and four days later the dog exhibited severe symptoms of insufficiency. They found that the interval between cessation of extract injections and development of adrenal insufficiency was somewhat prolonged by the feeding of sodium chloride, but concluded that the sodium chloride and water could not be regarded as an effective substitute for the cortical hormone in the bilaterally adrenalectomized dog since it was necessary to inject cortical extract to save the animals when they sooner or later developed severe symptoms.

Zwemer [32] reported similar results on a series of completely adrenalectomized cats. The average length of life in the control group was 10 days, while the average survival period of the experimental animals, which were treated with a number of different sodium compounds, was 18.4 days.

It appears from this experimental work, therefore, that as far as animals are concerned, the administration of sodium compounds alone without cortical extract in adrenal insufficiency will increase the span of life to some degree but not indefinitely; and that sodium salts are therefore not substitutes for the cortical extract. In some animals, however, the presence of accessory adrenal glands (as in rats) makes the adrenal insufficiency only a relative matter, and in such cases the sodium compounds, by delaying the appearance of the symptoms, will allow time for this accessory gland substance to hypertrophy sufficiently to permit the animals to survive indefinitely.

Clinically, however, sodium medication alone seems to have been more successful. Loeb's [19] original classic patient is still feeling well after two years on salt, and of the eight patients he has studied since 1932, six are still alive in fairly good health. Our patient has been in good health for over six months, and others have reported similar results. Harrop and associates [21] kept four patients symptomless for nine months with sodium medication and a cortical extract that was too weak to prolong the lives of adrenalectomized dogs. The death of Blankenhorn and Hayman's [33] patient in spite of 16 grams of sodium chloride daily is less encouraging, although a bronchopneumonia complicated the picture. The fact that Snell's [23] patient had been consuming salt excessively for several years before receiving medical attention may partially explain the unusually long duration of that case. Whether sodium salts alone will suffice to keep patients alive indefinitely remains to be seen, and depends, perhaps, on the hypertrophy of the remaining undiseased portions of the adrenal glands in the individual case.

The Dosage of Sodium Chloride

In treating Addison's disease with sodium chloride it is recommended that the dosage of salt be large: 10 to 15 grams a day.[37] Loeb [20] treated a

case with 20 grams daily, and the Holland investigators [26] have used as much as 35 grams daily. Divided doses seem to be most suitable, given either in milk, capsules, or tablets. We have had considerable success with plain uncoated one gram tablets. Enteric-coated tablets should be used with caution, as the coating may fail to dissolve.[25]

In some patients it may not be possible to maintain health without the use of cortical extract, and others at first maintained satisfactorily on salt alone may later need the glandular preparation, but the dose of the extract in such cases is likely to be much smaller than if no additional salt were given. The extract of the anterior lobe of the pituitary should be tried in addition in refractory cases, as suggested by Wilder.[27]

Case Report

A. G., aged 39, an Italian male, was admitted to the University Hospital, December 9, 1934, complaining of nausea, vomiting, chills, fever, and extreme weakness of 48 hours' duration.

His family history failed to reveal any hereditary tendencies. His past history showed: pneumonia at 17 years of age; malaria at 24 years of age; and an appendectomy at 30 years of age. Otherwise he had been well until the present illness. He denied venereal disease. The patient has lived in the United States for 11 years, and has a wife and four children, living and well.

The patient stated that he had suffered from a similar attack in May 1932, which confined him to his bed for one month. Shortly after the onset of this original attack he noticed increasing prostration and darkening of his skin. Except for these two manifestations his condition remained unchanged until June 1934 when he was again confined to his bed with extreme weakness, and remained prostrated throughout the month of July. In August, notwithstanding the increasing fatigue, he worked as a laborer for the County Welfare Organization, but found the exertion required a great effort. Finally he became so weak that he could not continue. On December 8, 1934, the day before admission to the hospital, he suddenly developed an acute episode consisting of bowel movements every 20 minutes associated with frequent attacks of vomiting, severe chills, marked dyspnea, excessive perspiration, and generalized aches and pains.

The patient was admitted to the hospital by ambulance, acutely ill and in a state of collapse. The significant findings on physical examination were extreme prostration, emaciation and dehydration; marked pigmentation of the face, hands, axillae, elbows, knees, buccal membrane, and anal margin; feeble, distant heart sounds; blood pressure 58 systolic and 36 diastolic; flat abdomen; temperature elevated to 100 degrees; and radial pulse of 80 beats per minute. A diagnosis of Addison's disease was made, and a clysis of glucose and normal saline was given immediately. Laboratory studies on admission revealed hemoglobin 110; red cells 5,400,000; white cells 8,000; non-protein nitrogen 75 mg. per cent; blood sugar 95 mg. per cent; chlorides 335.1 mg. per cent; serum protein 6.1, albumin 5, globulin 1. The urine contained acetone, diacetic acid, albumin, red cells, and granular and hyaline casts. Roentgen-ray evidence of an old tuberculous lesion affecting the upper right lung field was reported, but no calcified areas could be visualized in the kidney regions.

For the following six days he was given frequent clyses of glucose and normal saline, with slight improvement at first so that there was less nausea, vomiting, and restlessness. During this interval the blood pressure rose temporarily to 86 systolic and 58 diastolic, and then fell steadily to 73 systolic and 50 diastolic; the non-protein nitrogen remained elevated, and the blood chlorides continued below normal. On

the night of December 17, eight days after admission, the patient became irrational, got out of bed, and attempted to get into bed with another patient. This episode occurred after a restriction of fluids. The following day two grams of sodium chloride were given every four hours with decided improvement, so that within 24 hours the patient was coöperative and cheerful. The non-protein nitrogen was then 46, and the blood pressure 89 systolic and 57 diastolic, with marked improvement in the condition of the patient, and at the end of 72 hours he was sitting up in bed reading. The sodium chloride was increased to 15 grams daily, whereupon the non-protein nitrogen became normal and the blood chlorides increased to 366.6 mg. per cent.

One week later the patient was in excellent health, feeling better than he had for many months. At this point it was decided to confirm the diagnosis with a salt-poor diet. He was placed on this regime and all other medication was withheld. Within 12 hours he complained of increasing fatigue, which was followed by extreme restlessness and marked prostration. His sufferings excited the sympathy of a fellow ward patient who gave him a salt shaker when the attendants were not watching.

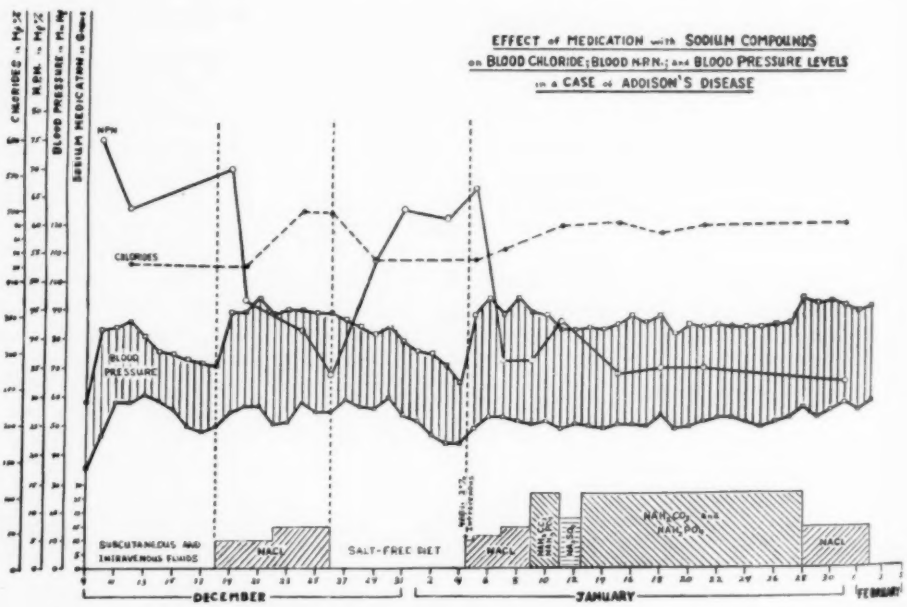

FIG. 1. The typical low blood pressure and chloride levels and the elevated N.P.N. in Addison's disease are relatively unaffected with fluids alone, but with sodium chloride are quickly restored to normal. The salt-poor diet confirms the diagnosis by reëstablishing the original disease levels. Sodium medications other than the chloride prove equally efficacious in maintaining the values at normal levels. (The blood chloride and non-protein nitrogen levels were determined in every case after an overnight fast. The blood pressure values were calculated as an average of 9 to 12 readings over a period of 24 hours starting at 8 a.m. each day. All medications were given in 6 equal doses daily at 6, 9, 12, 3, 6, and 9 o'clock respectively. The sodium chloride was administered in 1 gram uncoated tablets; the sodium bicarbonate and sodium biphosphate were first given in tablet form, but the size of each dose made this unsatisfactory; later the bicarbonate was given as a powder followed by the biphosphate in solution with syrup of sarsaparilla, proving to be a convenient method of administration. The sodium sulphate was given in 2 gram capsules, but was discontinued because of the effect on the bowel. The subcutaneous and intravenous fluids consisted of physiological saline and 5 per cent glucose. The salt-poor diet consisted of the usual house diet with certain foods of high salt content exempted, served without a salt shaker. The chloride values are given as chloride in plasma.)

The following day further restriction of salt was attempted, and the patient soon exhibited marked dyspnea and restlessness, profound prostration, anorexia and vomiting. The blood pressure dropped to 65 systolic and 44 diastolic and the non-protein nitrogen returned to 66.

The effect of the salt-poor diet was thought sufficiently conclusive to terminate the test at this point. Four hundred c.c. of a 2 per cent sodium chloride solution were given intravenously with marked subjective improvement within several hours. The patient was then returned to 15 grams of sodium chloride daily by mouth, and in three days was again in good health.

It was decided to demonstrate the specificity of the sodium ion by substituting other sodium salts for the chloride. Sodium sulphate was used, but soon proved unsatisfactory because of the effect on the bowel. Sodium bicarbonate as a powder, and sodium biphosphate in solution with syrup of sarsaparilla were then given in quantity sufficient to supply sodium equal to that in 15 grams of sodium chloride. The patient continued to improve on this therapy for 18 days. The blood chemistry studies re-

TABLE I

Effect of Medication with Sodium Compounds on Blood Chloride; Blood Non-Protein Nitrogen; and Blood Pressure Levels in a Case of Addison's Disease

Date	N.P.N. mg. %	Chlorides* as Cl mg. %	Average Blood Pressure mm. of mercury		Medication
			Systolic	Diastolic	
12–9–34	—	—	58	36	Subcutaneous and intravenous fluids
10	75	—	83	47	
11	—	—	84	58	
12	63	335.1	86	58	
13	—	—	81	61	
14	—	—	76	59	
15	—	—	75	56	
16	—	—	73	50	
17	—	—	72	48	
18	—	—	71	50	10 grams NaCl daily by mouth
19	70	—	89	55	
20	46	332.9	89	57	
21	—	—	94	57	
22	—	—	88	51	15 grams NaCl daily by mouth
23	—	—	90	52	
24	41	366.6	90	58	
25	—	—	88	55	
26	34	366.6	88	55	Salt-poor diet started
27	—	—	86	59	
28	—	—	84	57	
29	54	337.2	82	56	
30	—	—	84	60	
31	63	—	79	54	
1–1–35	—	—	76	52	
2	—	—	75	47	
3	61	—	71	44	
4	—	—	65	44	400 c.c. 2% NaCl intrav., 12 grams
5	66	337.2	88	49	NaCl daily by mouth
6	—	—	94	53	
7	36	343.7	88	53	15 grams NaCl daily by mouth
8	—	—	94	52	

TABLE I (Continued)

Date	N.P.N. mg. %	Chlorides* as Cl mg. %	Average Blood Pressure mm. of Mercury		Medication
			Systolic	Diastolic	
9	36	—	89	51	9 gm. NaH_2CO_3 and 18 gm. NaH_2PO_4 daily by mouth.
10	—	—	88	52	
11	43	361.0	83	49	18 grams Na_2SO_4 daily by mouth
12	—	—	83	51	
13	—	—	84	50	9 gm. NaH_2CO_3 and 18 gm. NaH_2PO_4 daily by mouth
14	—	—	83	49	
15	34	361.0	85	51	
16	—	—	88	51	
17	—	—	86	50	
18	35	358.1	88	54	
19	—	—	82	49	
20	—	—	85	50	
21	35	361.0	84	52	
22	—	—	85	53	
23	—	—	84	53	
24	—	—	84	52	
25	—	—	84	50	
26	—	—	85	52	
27	—	—	86	53	
28	—	—	95	57	15 grams NaCl daily by mouth
29	—	—	93	53	
30	—	—	93	56	
31	33	361.0	92	58	
2–1–35	—	—	90	56	
2	—	—	92	59	

* Plasma.

vealed normal findings, and the blood pressure remained 85 systolic and 52 diastolic throughout the period. The serum protein, the albumin-globulin ratio, the carbon dioxide combining power of the blood, the glucose tolerance test, and the basal metabolic test were all within normal limits. The specificity of the sodium ion was apparent.

The patient was then returned to 15 grams of sodium chloride daily, and after another week of continued good health was discharged on a maintenance dosage of 12 grams a day. Because of the expense of supplying sodium chloride in tablet form, the municipal dispensary placed the patient on 12 grams by mouth in bulk. On this the patient soon developed oral and gastric distress, and lapsed into a state of restlessness and weakness. He was quickly restored to excellent health by substituting 1 gram tablets for the bulk salt. The patient has continued to take his medication daily, and has remained well for nearly six months at this writing.* Figure 1 and table 1 show the effect of sodium medication on the blood chloride, blood non-protein nitrogen, and blood pressure levels in this case.

The 11 cases of Addison's disease treated with sodium compounds, which are summarized in the body of this article, represent the previously

* April 1936: Fourteen months after discharge our patient is in excellent health, with a blood pressure systolic 110, diastolic 74. He is faithfully taking 12 grams of sodium chloride each day.

published cases as determined by a search of the literature. The effect of sodium medication on the blood sodium level in nine of these is shown in figure 2 and in table 2.

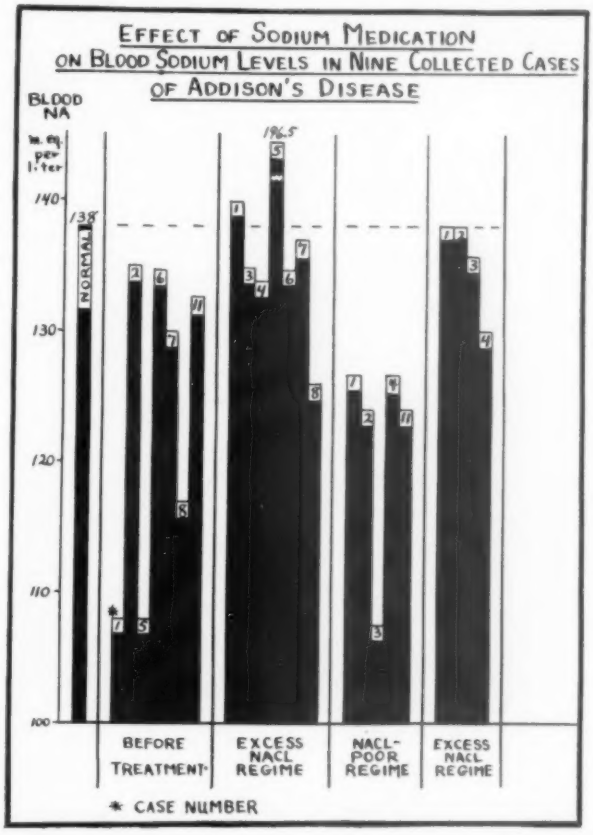

FIG. 2. The blood sodium levels in nine cases of Addison's disease collected from the literature were below normal before any treatment with sodium compounds was instituted. On an excess salt régime there was a rise in the level in every instance except in case 6, where the value was unchanged. There was a fall in the level in all cases on a salt-poor régime, and a rise toward normal in all when excess salt was again given. (The blood sodium levels of the various authors have been converted to milli-equivalents per liter in order that this comparison could be made. The milligram per cent values are given with the case summaries. The sodium is expressed as sodium in plasma, not whole blood. The normal value of 138 milli-equivalents per liter is that given by Loeb.[18])

CONCLUSIONS ON THE RELATION OF SODIUM TO ADRENAL DYSFUNCTION

1. The sodium level in the blood serum is found to be considerably decreased in bilaterally adrenalectomized animals.

2. In patients suffering from Addison's disease a similar decrease in the sodium level of the blood serum is present.

3. Sodium solutions will prolong the life of adrenalectomized animals, and when used with cortical extract, the amount of cortical preparation re-

TABLE II
Effect of Sodium Medication on Blood Sodium Levels in Nine Collected Cases of Addison's Disease

Case *	Author	Blood Sodium Levels in Milligrams Per Cent; Normal 138			
		Before Treatment	Excess NaCl Régime	NaCl-Poor Régime	Excess NaCl Régime
1	Loeb [18, 19]	107.8	139.9	126.8	138.0
2	Loeb, et al.[20]	135.0	—	124.0	138.0
3	Harrop, et al.[21]	—	134.8	106.6	135.8
4	Harrop, et al.[21]	—	133.9	126.8	130.0
5	Sears [22]	107.8	196.5	—	—
6	Snell [23]; Wilder [27]	134.7	134.7	—	—
7	Howell [24]	130.0	137.0	—	—
8	Nettrour and Rynearson [25]	117.5	126.2	—	—
11	Loeb, et al.[19b]	132.6	—	124.0	—

* Case numbers refer to the order of case summaries in this article.

quired is much diminished. Sodium solutions alone will not prolong the life of adrenalectomized animals indefinitely, unless accessory glands are present and hypertrophy sufficiently to supply adequate cortical hormone. Sodium compounds therefore are not a substitute for cortical extract but an adjuvant.

4. Sodium administered to patients with Addison's disease will either render them symptomless, or else minimize the amount of cortical extract required to maintain them in relatively good health. In some cases sodium alone will bring about a complete remission of a severe relapse. Several patients treated with sodium salts alone still continue to remain well after more than a year, and the span of life of many other patients to date seems to have been indefinitely prolonged.

5. The loss of cortical hormone in Addison's disease apparently removes the normal regulatory mechanism of the blood sodium level, which consequently falls, initiating the train of symptoms known as adrenal insufficiency. An associated secondary deficiency in the hormone from the anterior lobe of the pituitary body has recently been suggested.

6. A confirmatory test for Addison's disease of considerable value is the salt-poor diet, which will provoke a typical crisis in a true case of adrenal insufficiency and thereby aid in establishing the diagnosis.

SUMMARY

1. The treatment of Addison's disease by the Muirhead régime, and by cortical extract substitution therapy is briefly outlined.

2. The experimental and clinical evidence of the value of medication with sodium compounds in this disease is reviewed.

3. A case of Addison's disease which illustrates the beneficial thera-

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds

(One Original Case and 11 Collected from the Literature)

Case	Author	Observation Interval	Clinical Findings	Blood Pressure	Blood Serum Electrolyte Levels*						Treatment Prescribed
					Sodium		Chloride		Potassium		
					me./lit. normal 138	mg. % normal 317.4	me./lit. normal 103	mg. % normal 365.6	me./lit. normal 4.8	mg. % normal 18.7	
1.	Loeb [18]	7-19-32: Admission.	Progressive weakness; anorexia; loss of weight; increasing pigmentation of skin, nipples, and buccal membranes; mild secondary anemia.	90/60	123.5	284	88.6	314.5	5.3	20.7	Observation.
		7-26-32: After 1 week of observation.	Condition severe; profound exhaustion; slight dyspnea; increasing nausea; recurrent vomiting.	65/48	107.8	247.9	72.7	258.0	7.1	27.7	NaCl 9.5 grams by proctoclysis and 5 grams in capsules daily; 10 c.c. eschatin.
		7-30-32: After 4 days on NaCl; discharged.	Striking improvement.	102/70	133.0	305.9	93.8	332.9	5.1	19.9	Liberal salt diet plus 1½ teaspoonfuls salt daily.
		11-14-32: After 3 mo. on NaCl.	Gained 11 pounds; doing housework; no vomiting.	112/74	139.9	321.7	107.3	380.9	4.6	17.9	Same treatment continued.
		1-17-33: After 5 mo. on NaCl.	Vomited once after strenuous work; puffy ankles at night and edema under eyes in morning; urine normal.	122/80	—	—	—	—	—	—	Placed on salt-poor diet to relieve edema.
		1-19-33: After 2 days on salt-poor diet.	Extreme prostration; forced to go to bed.	—	—	—	—	—	—	—	Salt-poor diet continued.
		1-24-33: After 7 days on salt-poor diet; readmitted.	Continuous vomiting; progressive weakness; loss of 7 pounds weight.	86/60	126.8	291.6	92.3	327.6	5.7	22.2	7 grams NaCl orally daily. Proctoclysis 200 c.c. physiological saline every 4 hours.
		1-27-33: After 3 days on NaCl.	Much improved.	—	—	—	—	—	—	—	Rectal taps stopped. Oral salt continued.
		1-30-33: After 6 days on NaCl; discharged.	Feeling very well; gained 4 pounds.	122/80	138.0	317.4	103.5	367.4	5.0	19.5	Oral salt continued.

* The blood serum electrolyte readings of the various authors have been expressed in terms of mille-equivalents per liter and in milligrams per 100 c.c. in order that comparisons can be made. The mille-equivalent values given by Loeb [18] are used as average normal readings. The sodium has been expressed as sodium, the chloride as chloride, and the potassium as potassium in every case. All values are plasma readings, not whole blood.

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

					Blood Serum Electrolyte Levels*						
1.	Loeb [19]	4-10-33: After 3 mo. on NaCl.	Feeling well.	—	138.0	317.4	104.4	370.6	4.8	18.7	Increased to 15 grams NaCl daily on own initiative.
		11-9-33: After 10 mo. on NaCl.	18 months after first admission: improvement maintained; complains only of feeling cold and tiring rather easily; pigmentation slightly decreased.	normal	138.0	317.4	104.2	369.9	4.8	18.7	15 grams NaCl daily continued.
		10-13-34: After 21 mo. on NaCl.	More than 2 years after first admission still relatively well.	—	—	—	—	—	—	—	NaCl continued.
2.	Loeb, et al.[20]	Before admission.	Past history of tuberculous hip and pleurisy with effusion. Irregular abdominal pain and occasional vomiting for 2 years. Increasing brown pigmentation for 1 year. Weakness and dyspnea with slight cough for 6 months.	112/80 to 76/50	—	—	—	—	—	—	None.
		Admission; placed on normal diet.	Up and about the ward for 18 days with nausea, occasional abdominal pain, slowly increasing weakness.	—	135	310.5	—	—	—	—	Salt-poor diet.
		After 2 days on salt-poor diet.	Much worse, with dizziness, nausea, increased prostration. Vomited 200 c.c. in 48 hours.	—	124	285.2	—	—	—	—	20 grams NaCl orally daily.
		After 2 days on NaCl.	Improved remarkably, out of bed.	—	—	—	—	—	—	—	Oral salt continued.
		After 5 days on NaCl; discharged.	Much improved.	—	138	317.4	—	—	—	—	Maintenance dosage 10 grams NaCl daily with highly salted diet.
3.	Harrop et al.[21]	Admission.	Known case of Addison's disease, with roentgen-ray evidence of calcification.	—	—	—	—	—	—	—	High salt diet and low potency cortical extract.
		After 9 months on high salt diet and low potency extract.	Patient symptomless, gaining weight and strength.	—	—	—	—	—	—	—	High salt diet and sterile hypo instead of extract.
		After 6 weeks on high salt diet and sterile hypo.	Relapse.	—	—	—	—	—	—	—	High salt diet and low potency cortical extract resumed.
		After several days on high salt diet and low potency extract.	Improved.	—	134.8	300.0	106.8	379.1	—	—	Low salt diet and low potency cortical extract.
		After 4 days on salt-poor diet and low potency extract.	Marked weakness and anorexia; severe relapse.	—	106.6	245.1	81.2	288.2	—	—	Low salt diet discontinued. Intravenous saline begun, cortical extract continued.

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

Case	Author	Observation Interval	Clinical Findings	Blood Pressure	Blood Serum Electrolyte Levels*						Treatment Prescribed
					Sodium		Chloride		Potassium		
					me./lit. normal 138	mg. % normal 317.4	me./lit. normal 103	mg. % normal 365.6	me./lit. normal 4.8	mg. % normal 18.7	
3.	Harrop et al. (*Cont.*)	After 9 days on salt and low potency extract.	Much improved.	—	128.2	294.8	96.8	343.6	—	—	High salt diet and cortical extract.
		After 18 days on salt and low potency extract.	Apparently normal.	—	135.8	302.3	102.4	363.5	—	—	High salt diet and cortical extract
4.	Harrop et al.[21]	Admission.	Known case of Addison's disease; feeling very well on high salt diet and low potency cortical extract.	—	133.9	307.9	103.6	367.7	—	—	High salt diet and cortical extract discontinued. Placed on salt-poor diet.
		After 5 days on salt-poor diet without extract.	Severe relapse.	—	126.8	291.6	95.2	337.9	—	—	11 grams NaCl daily.
		After 6 days on salt only.	Much improved.	—	130.0	299.0	100.0	355.0	—	—	11 grams NaCl daily.
5.	Sears[22]	1927.	Diagnosed Addison's disease.	—	—	—	—	—	—	—	None.
		1931.	Mild relapse.	—	—	—	—	—	—	—	Course of cortical extract injections.
		1932.	Increasing weakness, anorexia, vomiting, giddiness, precordial pain.	125/88	—	—	—	—	—	—	More extract given.
		3-10-34: Admission.	Recurrence 4 weeks before; with increasing weakness, giddiness, slight cough, and increasing pigmentation of axillae, nipples, back of neck, buccal membrane and palate.	120/80	107.8	248	75.5	268	14.3	56	Regular diet with 5 grams of NaCl daily.
		3-17-34: After 1 week on regular diet with 5 grams NaCl daily. Discharged.	Generally improved; weakness gone; able to get about without difficulty.	140/85	196.5	452	128.1	455	4.1	16	Advised to continue NaCl.
6.	Snell[23]	1911 to 1923.	Bilateral pulmonary tuberculosis in early life. 1917: diffuse pigmentation of skin. 1922: weakness. 1923: severe continuous lumbar pain.	—	—	—	—	—	—	—	None.

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

6.	Snell (*Cont.*)	1923 to 1929.	Extreme weakness; increased pigmentation; palpable cervical glands; râles in both apices; roentgen-ray of lungs positive on admission in 1923. Improved sufficiently on Muirhead régime to go home in 2 weeks, where it was continued. 1924: tuberculous adenitis proved at biopsy; radium treatment. 1929: in good health, Muirhead treatment stopped.	110/80 100/75	—	—	—	—	—	—	Muirhead treatment: epinephrine orally, rectally, and subcutaneously at frequent intervals up to patient's tolerance daily; with 'desiccated cortex' orally 10 to 15 grains daily.
		1929 to 1934.	1932: failing strength, increasing fatigue; marked craving for salty food. March 1934: losing weight.	—	—	—	—	—	—	—	None.
		5-16-34: Admission.	Marked weakness, confusion, loss of memory, severe constipation; pigmentation of exposed surfaces, oral mucosa, and genitalia; weak faint heart; both adrenals calcified on roentgen-ray.	110/65	134.7	310.0	92.9	330.0	4.9	19.3	Intramuscular cortical extract (Kendall); sodium chloride 10 grams orally; and 1 liter physiologic saline daily.
		After several days discharged.	Much improved in 24 hours; followed by gain in weight, increased appetite and strength.	—	134.7	310.0	105.8	375.6	4.9	19.3	10 grams NaCl daily recommended on discharge.
	Wilder [27]	July 1934, after 2 months on 10 grams NaCl daily.	Well for 2 months. Admitted again in mild crisis; improved with treatment; discharged.	—	—	—	—	—	—	—	6 c.c. cortin; 8 grams of salt pills, and salt diet daily.
		9-30-34: Admission after 2 months on 6 c.c. cortin, and 8 grams NaCl daily plus salt diet.	Severe crisis with abdominal pain, nausea, vomiting, restlessness, hiccough, and extreme weakness.	—	—	—	—	—	—	—	Cortin and 0.9% NaCl by vein for 2 days; then 6 mg. cortin and 8 grams NaCl in pills, plus 6 grams in diet daily.
		10-4-34: After cortin and NaCl intravenously and orally.	Out of bed but still weak and restless.	—	—	—	—	—	—	—	0.3 c.c. anterior pituitary extract daily in addition.
		10-9-34: After 5 days on cortin, NaCl, and anterior pituitary.	Marked improvement, stronger than in many months.	—	—	—	—	—	—	—	Salt pills omitted, receiving only 6 grams NaCl in diet; cortin and anterior pituitary extract continued.
		10-14-34: After 4 days on cortin and anterior pituitary only.	Weaker, with nausea and hiccough.	—	—	—	—	—	—	—	NaCl by vein; daily salt pills resumed; cortin continued; anterior pituitary extract stopped.
		10-23-34: After 8 days on cortin and NaCl.	Improved; some residual weakness.	—	—	—	—	—	—	—	Salt again restricted to diet; cortin continued.

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

Case	Author	Observation Interval	Clinical Findings	Blood Pressure	Blood Serum Electrolyte Levels *						Treatment Prescribed
					Sodium		Chloride		Potassium		
					me./lit. normal 138	mg. % normal 317.4	me./lit. normal 103	mg. % normal 365.6	me./lit. normal 4.8	mg. % normal 18.7	
6.	Wilder (*Cont.*)	10-25-34: After 2 days on cortin and limited NaCl.	Marked weakness, with hiccough and nausea.	—	—	—	—	—	—	—	Intravenous NaCl given; daily salt pills resumed; cortin continued.
		10-27-34: After 2 days on cortin and full NaCl as before.	Symptom-free.	—	—	—	—	—	—	—	Cortin discontinued; NaCl as before, and 0.3 c.c. anterior pituitary extract given daily.
		11-2-34: After 6 days on NaCl and anterior pituitary extract; no cortin.	Failing rapidly.	—	—	—	—	—	—	—	Cortin resumed, with daily NaCl, and anterior pituitary extract.
		11-9-34: After 7 days on NaCl, cortin, and anterior pituitary extract.	In good health.	—	—	—	—	—	—	—	Same treatment continued.
7.	Howell [24]	1933: Before admission.	August 1933: pigmentation of skin. November 1933: weakness; lassitude; anorexia; dyspnea on slight exertion; swelling of ankles.	—	—	—	—	—	—	—	None.
		2-14-34: Admission.	Extreme exhaustion; nausea; vomiting; loss of 56 pounds weight; characteristic pigmentation on buccal membranes; weak heart and pulse; mild secondary anemia.	60/40 78/48	130.0	298.0	—	—	—	—	Observation.
		2-23-34: After 1 week of observation.	Condition unchanged + nausea; listless; apathetic.	—	—	—	—	—	—	—	10 grams NaCl daily.
		2-24-34: After 24 hours on 10 grams NaCl daily.	Dramatic effect: sitting up reading; appetite improved; nausea gone.	—	—	—	—	—	—	—	10 grams NaCl daily continued.
		3-9-34: After 14 days on 10 grams NaCl daily.	Patient allowed up. Had not felt as well in months.	—	130.8	301.0	—	—	—	—	Salt continued.
		3-15-34: After 19 days on 10 grams NaCl daily.	Patient in good health.	—	—	—	—	—	—	—	NaCl reduced to 5 grams daily without patient's knowledge.

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

7.	Howell (*Cont.*)	3-19-34: After 4 days on 5 grams NaCl daily.	No subjective changes noted.	—	137.0	315.0	—	—	—	—	5 grams NaCl daily continued.
		3-26-34: After 11 days on 5 grams NaCl daily.	Weakness; loss of appetite; vomited several times.	—	—	—	—	—	—	—	Returned to 10 grams NaCl daily.
		4-5-34: After 10 days on 10 grams NaCl daily. Discharged.	Marked improvement.	75/45	—	—	—	—	—	—	To continue NaCl.
8.	Nettrour and Rynearson [25]	1932 to 1934: Before admission.	1932: progressive fatigue; 'too tired to study'; failed in college. Feb. and Apr. 1934: acute upset with slight cough; nausea; vomiting; slight questionable jaundice; extreme weakness; loss of 18 pounds weight.	—	—	—	—	—	—	—	None.
		8-4-34: Admission.	Thin, tired male: no definite pigmentation; mild anemia; adrenals not calcified; chest roentgen-ray negative; B.M.R. −27 and −22.	78/52 106/68	117.5	271.4	95.9	340.4	5.1	20.2	Placed on salt-poor diet to aid in diagnosis.
		8-9-34: After 5 days on salt-poor diet.	Nausea; vomiting; and extreme weakness.	86/50	—	—	83.2	295.5	—	—	Intravenous saline, 10 c.c. cortical extract daily first 2 days; 8 gm. NaCl daily by mouth
		8-13-34: After 4 days on NaCl and cortical extract.	Patient improved: no weakness, headache, epigastric distress, nausea, or vomiting.	—	126.2	290.4	89.7	350.7	—	—	8 grams NaCl daily continued.
9.	Wilder [27]	1913 to 1934.	1913: acute tuberculous salpingitis and peritonitis. 1929: found to be essentially well. Fall 1933: fatigue, anorexia, loss of weight, black freckles, and pigmentation of gums.	—	—	—	—	—	—	—	None.
		February 1934.	Diagnosed Addison's disease.	—	—	—	—	—	—	—	Salt pills 8 grams daily.
		9-27-34: After 7 mo. on salt; admission.	Condition unchanged.	—	—	—	—	—	—	—	Salt-poor diet to confirm diagnosis.
		9-29-34: After 2 days on salt-poor diet.	Nausea, hiccough; sudden collapse with severe abdominal pain and cyanosis.	—	—	—	—	—	—	—	20 grams NaCl and 20 milligrams of cortin by vein.
		9-30-34: After cortin and NaCl by vein.	Much improved in 24 hours.	—	—	—	—	—	—	—	10 mg. cortin daily; salt restricted to diet (6 grams).
		10-2-34: After 3 days on cortin and limited NaCl.	Prostrated; acutely ill.	—	—	—	—	—	—	—	Cortin 6 mg.; anterior pituitary extract 0.3 c.c.; total NaCl 14 grams daily.

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

Case	Author	Observation Interval	Clinical Findings	Blood Pressure	Blood Serum Electrolyte Levels*						Treatment Prescribed
					Sodium		Chloride		Potassium		
					me./lit. normal 138	mg. % normal 317.4	me./lit. normal 103	mg. % normal 365.6	me./lit. normal 4.8	mg. % normal 18.7	
9.	Wilder (*Cont.*)	10-9-34: After 7 days on cortin, NaCl, and anterior pituitary extract.	Marked improvement: symptom-free; with increased endurance, gain in weight.	—	—	—	—	—	—	—	Cortin and anterior pituitary continued; salt restricted to diet (6 grams).
		10-17-34: After 8 days on anterior pituitary, and cortin; NaCl restricted.	Weakness, restlessness, and nausea.	—	—	—	—	—	—	—	Salt by mouth and vein; cortin continued; anterior pituitary extract discontinued.
		10-22-34: After 5 days on cortin and NaCl.	In good health.	—	—	—	—	—	—	—	Salt restricted; 6 mg. cortin continued.
		10-24-34: After 2 days on cortin only.	Extreme weakness, nausea, and hiccough.	—	—	—	—	—	—	—	Salt, cortin, and anterior pituitary resumed daily.
		10-30-34: After 6 days on cortin, NaCl and anterior pituitary extract.	In good condition.	—	—	—	—	—	—	—	Cortin stopped; anterior pituitary and NaCl continued.
		11-3-34: After 4 days on anterior pituitary and NaCl, no cortin.	Weakness, nausea, restlessness, loss of weight.	—	—	—	—	—	—	—	Cortin resumed; anterior pituitary and NaCl continued.
10.	Blankenhorn and Hayman [33]	9-9-33: Admission.	Pigmentation of skin, palate, gums, and buccal membrane; vomiting; weakness; loss of weight for 3 months; roentgen-ray calcification over upper pole of left kidney. Diagnosed Addison's disease.	108/55	—	—	87.3	310.0	—	—	Full diet and salt ad lib.
		9-12-33: After 3 days on full diet and salt ad lib.	Severe crisis: repeated vomiting, irrational.	80/40	—	—	—	—	—	—	750 c.c. physiologic saline intravenously.
		9-13-33: After 1 day on normal saline by vein.	Temporary improvement, followed by vomiting, with patient still irrational.	—	—	—	76.1	270.0	—	—	2250 c.c. saline subcutaneously and intravenously.
		9-14-33: After 2 days on normal saline by vein and under skin.	Marked improvement.	—	—	—	—	—	—	—	12 grams NaCl daily in capsules.

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

10.	Blankenhorn and Hayman (*Cont.*)	10-1-33: After 17 days on NaCl.	Continued improvement.	110/75	—	—	94.3	335.0	—	—	12 grams NaCl daily continued.
		10-3-33: After 19 days on NaCl.	In good condition.	—	—	—	—	—	—	—	Placed on salt-poor diet to confirm diagnosis.
		10-5-33: After 2 days on salt-poor diet.	Despondent, irritable; voluntarily remained in bed.	110/75	—	—	—	—	—	—	Salt-poor diet continued.
		10-8-33: After 5 days on salt-poor diet.	Mental condition worse, nauseated.	105/80	—	—	89.3	317.0	—	—	Salt-poor diet continued.
		10-11-33: After 8 days on salt-poor diet.	Condition grave.	85/55	—	—	82.2	292.0	—	—	30 c.c. cortical extract with salted food, next day same with 30 c.c. intramuscularly.
		10-13-33: After 2 days of cortical extract treatment.	No improvement.	—	—	—	74.9	266.0	—	—	Glucose and saline intravenously.
		10-14-33: After 1 day on glucose and saline by vein.	Definite improvement in 12 hours, marked in 36 hours.	—	—	—	78.9	280.0	—	—	12 grams NaCl daily in capsules resumed.
		10-16-33: After 3 days on NaCl.	Out of danger.	—	—	—	92.1	327.0	—	—	NaCl continued.
		10-23-33: After 10 days on NaCl.	In good health, pigmentation faded.	105/75	—	—	—	—	—	—	NaCl continued.
		11-5-33: After 22 days on NaCl.	In excellent condition.	—	—	—	—	—	—	—	NaCl stopped. Mixture of NH_3, Ca, and K chlorides substituted.
		11-8-33: After 3 days on NH_3, Ca, and KCl mixture.	Abdominal pain, nausea, and vomiting.	90/50	—	—	—	—	—	—	Intravenous saline, then 12 grams NaCl daily.
		11-9-33: After 1 day on NaCl.	Immediate improvement.	—	—	—	—	—	—	—	NaCl continued.
		11-23-33: After 14 days on NaCl.	In good condition.	—	—	—	—	—	—	—	NaCl stopped. Mixture of sodium sulphate, sodium bicarbonate and sodium biphosphate substituted.
		12-10-33: After 17 days on sodium salts other than chloride. Discharged.	No discomfort. Patient continued to feel very well.	—	—	—	—	—	—	—	Placed on full diet with 16 grams NaCl daily in capsules.

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

Case	Author	Observation Interval	Clinical Findings	Blood Pressure	Blood Serum Electrolyte Levels*						Treatment Prescribed
					Sodium		Chloride		Potassium		
					me./lit. normal 138	mg. % normal 317.4	me./lit. normal 103	mg. % normal 365.6	me./lit. normal 4.8	mg. % normal 18.7	
10.	Blankenhorn and Hayman (*Cont.*)	12-20-33: After 10 days on NaCl.	Feeling strong; good appetite.	120/80	—	—	—	—	—	—	16 grams NaCl continued.
		1-4-34: After 25 days on NaCl.	Appetite poor; sleepless; irritable; confused; profound crisis. Developed bronchopneumonia and died, no postmortem.	—	—	—	122.2	434.0	—	—	Saline and glucose intravenously; 20 c.c. cortical extract intravenously.
11.	Loeb et al.[18b]	Admission.	Classical signs and symptoms of Addison's disease for 8 months. Severe anorexia and weakness past 2 weeks.	82/60	132.6	304.9	—	—	—	—	Salt-poor diet.
		After 5 days on salt-poor diet.	Increasing weakness, drowsiness, and anorexia for 4 days; sudden crisis: semi-comatose, imperceptible pulse, blood sugar 48, ketosis present.	58/50	129.4	297.6	—	—	—	—	25 c.c. cortical extract intravenously; frequent epinephrine injections; continuous infusion salt solution and dextrose.
		After 24 hours of infusion treatment.	No change in condition, shock persisting. Blood sugar normal, ketosis absent.	62/40	124.0	285.2	—	—	—	—	Continuous infusion of salt solution and dextrose continued.
		After 7 days of infusion treatment.	General health greatly improved, vomiting stopped; strength and appetite returning.	—	—	—	—	—	—	—	Regular diet with 10 grams NaCl daily.
12.	Reifenstein and Reifenstein	1932 to 1934.	May 1932: nausea, vomiting, chills, fever, and extreme weakness. Fall 1932: bronze pigmentation of skin. June–July 1934: in bed with extreme weakness. August 1934: increasing fatigue. Dec. 8, 1934: acute diarrhea, vomiting, prostration.	—	—	—	—	—	—	—	None.
		12-9-34: Admission.	Acutely ill in state of collapse: nausea, vomiting, chills, dyspnea, excessive perspiration, diarrhea, and generalized weakness. Pig-	58/36	—	—	94.4	335.1	—	—	Glucose and normal saline subcutaneously and intravenously.

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—*Continued*

12.	Reifenstein and Reifenstein (*Cont.*)		mentation of face, hands, axillae, and buccal membranes; feeble heart sounds; roentgen-ray showed old pulmonary tuberculosis, adrenals not calcified; hemoconcentration; NPN 75. Diagnosed Addison's disease.								
		12-18-34: After 9 days on subcutaneous and intravenous fluids.	Slight improvement at first with less nausea, vomiting, and restlessness. Later definitely worse, completely irrational, NPN still elevated.	86/58 73/50	— —	— —	— 93.8	— 332.9	— —	— —	10 grams NaCl daily; after 4 days increased to 15 grams daily.
		12-26-34: After 8 days on NaCl.	Definite improvement in 24 hours: patient sane and cheerful. Marked change in 4 days, with patient out of bed. NPN 34. In 1 week felt better than he had in months.	89/57	—	—	103.3	366.6	—	—	Placed on salt-poor diet to confirm diagnosis.
		1-4-35: After 9 days on salt-poor diet.	Increasing fatigue, extreme restlessness, marked prostration in 12 hours; anorexia and vomiting in 3 days. NPN 66. Condition rapidly becoming grave.	65/44	—	—	95.0	337.2	—	—	Intravenous of 400 c.c. 2% NaCl; then 12 to 15 grams NaCl daily.
		1-8-35: After 4 days on NaCl.	In good health again; up and about.	94/52	—	—	96.8	343.7	—	—	NaCl stopped. 9 grams sodium bicarbonate and 18 grams sodium biphosphate orally daily.
		1-27-35: After 19 days on sodium bicarbonate and sodium biphosphate.	Patient continued to improve; felt very well. Apparently normal to all tests.	85/52	—	—	101.7	361.0	—	—	Returned to 15 grams NaCl daily.
		2-2-35: After 6 days on NaCl; discharged.	In excellent health.	92/59	—	—	101.7	361.0	—	—	Placed on maintenance dosage of 12 grams NaCl daily in tablet form.
		6-18-35: After 6 mo. on sodium medication.	Still in good health.	—	—	—	—	—	—	—	NaCl continued.
		4-3-36: After 15 mo. on sodium medication.	Still in excellent health.	110/74	—	—	—	—	—	—	NaCl continued.

peutic effect of sodium medication, the value of the confirmatory salt-poor diet test, and the specificity of the sodium ion in treating this disease is presented.

4. Eleven other cases treated with sodium collected from the literature are summarized.

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THE LEUKOCYTE PICTURE IN HODGKIN'S DISEASE *

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ALTHOUGH Hodgkin's [1] disease was described by him as early as 1832, the blood picture in this disease was not seriously considered until 1910. At that time Fabian,[2] after a critical survey of the literature, reported that the blood picture was not sufficiently constant to be of any diagnostic value. He did state, however, that the most frequent hematologic finding in Hodgkin's disease was a moderate increase in the number of polymorphonuclear neutrophiles and a relative decrease in the number of lymphocytes.

In 1911, following this survey, Bunting [3] reported the analysis of a small series of blood counts in cases of Hodgkin's disease and described a specific blood picture for the diagnosis of the disease. He divided his cases into two distinct groups according to the differential count. In the first group, in which the disease had been present for less than a year, there was a normal or decreased percentage of polymorphonuclear neutrophiles; in the second group, in which the disease had been present for more than a year, there was marked leukocytosis with an increase in the number of polymorphonuclear cells from 72 to 90 per cent. The transitional cells or monocytes were increased in both groups; the lymphocytes were sometimes increased in the early cases but showed a steady decrease as the disease progressed. Bunting also maintained that on examination of the blood smear a definite increase in the number of platelets was found.

In 1914 Bunting [4] and Yates [5] reported an additional group of cases of Hodgkin's disease with the same hematologic findings. In the period from 1915 to 1920 these findings of Bunting's were generally confirmed in isolated reports of cases. Also reported in this period were rare cases in which eosinophilia was present. The relationship between leukemia, sarcoma, and Hodgkin's disease received considerable attention at this time. Although the blood smear was used for differential diagnosis in some instances, the pathologic changes observed in excised lymph nodes were the criteria for differential diagnosis.

In 1920, however, Longcope and McAlpin [6] in a comprehensive study of Hodgkin's disease stated that changes existed in the blood, which were so characteristic that they could be used to differentiate this disease from all other types of enlargement of lymph nodes. These constant changes consisted of a relative or absolute increase in the number of transitional cells (monocytes) and a total increase in the number of platelets throughout the

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course of the disease. Relative or absolute eosinophilia seemed to be most marked when there was necrosis of the lymph nodes.

Following this survey with Longcope, in 1923 McAlpin [7] studied 18 cases of Hodgkin's disease and arrived at conclusions somewhat contradictory to those of the earlier report. He stated that it would not be possible to diagnose Hodgkin's disease from examination of the blood smear. In this series of 18 cases the number of transitional cells was high in only eight cases and the platelets only in seven. When the cases were arranged in the order of their total leukocyte count there was no apparent relationship between this and the duration of the disease. The highest leukocyte count was 13,000 per cubic millimeter.

Weiss [8] in 1924 reversed the original idea of an increase in polymorphonuclear neutrophiles as being the most important finding and considered it to be instead the decrease in the number of lymphocytes. He stated that the neutrophiles and eosinophiles might be increased in number, and further suggested that a leukocytosis exceeding 20,000 cells per cubic millimeter warranted the suspicion that the diagnosis of Hodgkin's disease was incorrect.

The largest and most completely studied group of cases of Hodgkin's disease up to 1930 was reported by Falconer.[9] He had observed 40 cases, which he divided into two groups as Bunting had done. Falconer concluded that in the first group, in which the disease was of less than a year's duration, the total leukocyte and differential counts were within normal limits, whereas in the second group, in which the disease was of more than a year's duration, only a slight increase in the total leukocyte count occurred, with a slight increase in the percentage of polymorphonuclear cells at the expense of a decrease in the number of lymphocytes. Although Falconer had used Bunting's grouping of cases, his observations did not quite agree with the latter's. Falconer found, however, an average and fairly constant increase in the number of mononuclear cells. The eosinophile count averaged about normal or slightly below normal, although in one instance the percentage was very high. The platelet counts in Falconer's cases were not high.

Straube,[10] in 1931, summarized his findings in 21 cases of Hodgkin's disease. He decided that no uniform or diagnostic hematologic picture for Hodgkin's disease existed, and that it was therefore not possible to establish the diagnosis on the basis of hematologic examination alone.

Thus the views regarding the diagnostic value of the blood picture in this disease differ greatly. Some workers consider the blood picture to be characteristic of the disease, whereas others are of the opinion that no characteristic blood picture exists. If there is a characteristic blood picture, it must have to do with the differential leukocyte count, as most investigators have found that in regard to the erythrocytes in general, a slight secondary anemia exists which is not in itself characteristic.

The present study was therefore undertaken to determine the diagnostic value of the blood picture in Hodgkin's disease. Owing to the fact that the method of determining blood platelets was changed during the course of this study, the platelets were not considered.

Plan of Study

The differential counts were made from blood smears in cases in which a diagnosis of Hodgkin's disease or lymphosarcoma was confirmed by pathologic study of an excised lymph node. The criteria for the diagnosis of lymphosarcoma were: loss of normal architecture of the lymph node, absence of lymph follicles, and marked hyperplasia of the cellular elements; and for Hodgkin's disease: fibrosis, with an increase of connective tissue throughout the node, presence of Dorothy Reed cells, and an increase in the number of eosinophiles in the node.[11] None of the patients had had any previous treatment. The duration of the disease was noted, and the cases were divided into four groups depending on the state of the disease when the patient was admitted to the clinic. Group I included those cases in which the disease was of six months' duration or less, group II included those cases in which the disease was of more than six but not more than 12 months' duration, group III included those cases in which the disease was of more than a year's but not more than two years' duration, and group IV included those cases in which the disease was of more than two years' duration. The longest duration was 13 years. The cases were also divided into four groups according to the situation and extent of the disease: Group A in which a single cervical, supraclavicular, or axillary lymph node was involved, group B in which a single inguinal lymph node was involved, group C in which two cervical, axillary, or supraclavicular lymph nodes were involved or in which a single lymph node in two of these situations was involved, and group D in which there was general adenopathy.

Data

Sixty-five differential counts were made from blood smears in 40 cases of Hodgkin's disease and 18 differential counts were made from blood smears in nine cases of lymphosarcoma.

Group I. In 12 of 25 differential counts, or 48 per cent, the percentage of neutrophiles was greater than 68, the highest being 85. The shift to the left was not marked, the nonfilament count of the polymorphonuclear neutrophiles being only 8.1 cells in 200. The average percentage of lymphocytes was well within the normal limits of 25 to 30. In 15 of 25 counts, or 60 per cent, the percentage of lymphocytes was less than 25; in 20 per cent of the counts it was greater than 30. The average percentage of monocytes was within normal limits; in five counts, or 20 per cent, it was greater than eight. The average percentages of eosinophiles and basophiles were within normal limits, in one instance being 8.5.

Group II. In this group, in which the disease had existed from six months to one year, four of the 11 patients, or 36 per cent, had leukocyte counts higher than 8000, whereas two had counts lower than 5000 per cubic millimeter. The average percentage of polymorphonuclear neutrophiles was slightly higher than in group I but was at the upper limit of normal; in nine of 17 counts the percentage was greater than 70, whereas in two it was less than 60. The nonfilament count showed only a very slight increase over that in group I. The average percentage of lymphocytes was definitely decreased below normal, in 14 of 17 counts being less than 25. The average percentage of monocytes was slightly increased, in seven of 17 counts, or 41 per cent, being more than eight. The percentages of eosinophiles were all within normal limits.

Group III. Seven of the nine patients in this group, or 77.8 per cent, had leukocyte counts greater than 8000 per cubic millimeter. The greatest increase in the percentage of polymorphonuclear neutrophiles took place in this group. In 12 of 16 counts, or 75 per cent, this percentage was increased above 68. The shift to the left was almost doubled in this as compared to groups I, II, and IV. The average percentage of lymphocytes, on the other hand, was the lowest of any of these groups; of 16 counts on the nine patients in the group, 15, or 94 per cent, were below 25. In 16 counts of monocytes, or 25 per cent, the percentages were more than eight. The percentage of eosinophiles was 1.8, in all but two instances being within normal limits. The basophiles likewise were within normal limits.

Group IV. The leukocyte count in this group was the lowest of any of these groups. The average percentage of polymorphonuclear neutrophiles in this group could hardly be called abnormal; in four of the eight counts the percentage was above 68. The shift to the left or nonfilament count was slightly increased over the previous groups. The average percentage of monocytes was seven, with only two counts being above the normal eight. The average eosinophile count was the highest of any of the groups, although only two counts were above the normal of four.

The summary of groups I to IV, inclusive, is given in table 1.

Group A. In 20 of 28 counts, or 71 per cent, the percentage of polymorphonuclear neutrophiles was increased above the normal 68. The nonfilament count was the least in group A. In 23 of 28 counts, or 82 per cent, the percentage of lymphocytes was less than the normal of 25. The percentages of eosinophiles and basophiles were all within normal range.

Group B. The findings for this group were practically the same as for groups A, C, and D.

Group C. The average leukocyte count was the lowest of those in groups A to D, inclusive, in only one case being increased to more than 10,000 cells per cubic millimeter of blood. In only 33 per cent of the counts was the average percentage of polymorphonuclear neutrophiles above normal. The shift to the left or nonfilament count was slightly increased to 12 cells in 200. In two counts the percentage of lymphocytes was increased above

TABLE I

Summary of Average Leukocyte Counts in Groups I to IV, Inclusive

Group	Cases	Duration, years *	Leukocytes, per cubic millimeter	Nonfilament count, per cent	Differential count, per cent				
					Polymorphonuclear neutrophiles	Lymphocytes	Monocytes	Eosinophiles	Basophiles
I.	15	1/2 or less	7,693	8.1	63.8	27.2	5.9	1.9	0.7
II.	11	1/2 to 1	7,307	9.2	71.0	18.7	8.4	1.6	0.3
III.	9	1 to 2	11,055	16.0	75.3	14.8	7.2	1.8	0.6
IV.	5	2 to 13	6,940	12.3	69.8	18.8	7.0	3.8	1.0

* Exact limits of the groups are given in the text.

30, whereas in the others, with the exception of one case, it was practically within normal limits. The percentage of monocytes was increased in four counts whereas the average percentage was normal. The percentages of eosinophiles and basophiles were both within normal limits.

Group D. The average percentage of polymorphonuclear neutrophiles was normal; however, in 13 of 21 counts, or 61 per cent, the percentage of polymorphonuclear neutrophiles was slightly increased. The shift to the left was not marked. The average percentage of lymphocytes was slightly below normal, with 66 per cent of the counts being below 25. While the average monocyte count was normal, the percentage was increased above normal in 29 per cent of the counts. In two instances the percentage of eosinophiles was increased above the normal limits while the percentage of basophiles was normal.

The summary of groups A to D, inclusive, is given in table 2.

Cases of Lymphosarcoma. The findings in cases of lymphosarcoma differed only slightly from those in cases of Hodgkin's disease. In two cases in this group the leukocyte count was above 8000 per cubic millimeter. In 23.5 per cent of the counts the percentage of polymorphonuclear neutrophiles was increased above normal. Of the lymphocyte counts, 41 per cent were below normal, 29 per cent above normal. There was also an increase above normal in 18 per cent of the monocyte counts. In two counts, or 11 per cent, the percentage of eosinophiles was increased above normal. The basophile counts were increased in two instances.

COMMENT

From this study it appears that there is no specific morphologic blood picture diagnostic of Hodgkin's disease. Estimations of the number of

TABLE II

Summary of Average Leukocyte Counts in Groups A to D, Inclusive

Group	Extent of involvement	Cases	Leukocytes, per cubic millimeter	Nonfilament count, per cent	Differential count, per cent				
					Polymorphonuclear neutrophiles	Lymphocytes	Monocytes	Eosinophiles	Basophiles
A	Cervical, supraclavicular, or axillary (1 node) *	17	8,218	6.3	71.6	18.1	7.5	2.2	0.6
B	Inguinal (1 node)	5	10,480	17.0	74.6	17.6	5.9	1.4	0.4
C	Cervical, supraclavicular, or axillary (2 nodes) †	6	5,950	12.0	61.8	28.1	6.7	1.8	0.6
D	General adenopathy	12	8,517	9.3	67.5	22.6	6.8	2.4	0.7

* Only one node affected in any of these three situations.
† Two nodes affected in one of these situations or one node in each of two of these situations, namely, two cervical nodes, or one cervical and one axillary node, and so forth.

leukocytes per cubic millimeter of blood showed them to be within normal limits, as were also the various percentages in the differential counts (group I, table 1). It is true that in an occasional case there was a deviation from the normal of slight degree, but this in itself is without significance as the averages of the group were well within those recognized as normal. In group II, however, in which Hodgkin's disease was of slightly longer duration, there was definite polymorphonuclear leukocytosis with a decrease in the number of lymphocytes, as has been observed by other investigators. In these groups I and II there was no tendency toward a shift to the left of the neutrophiles, the values being well within normal limits, that is, 8.1 and 9.2 nonfilamented cells, respectively, per 100 neutrophiles.

In group III, in which the duration of the disease was longer, the most definite changes occurred. There was a definite but slight increase in the number of polymorphonuclear neutrophiles, a relative decrease in the number of lymphocytes, and an increase in the number of nonfilamented neutrophiles. This is probably due to the more widespread involvement of the body by the process, with inroads of sufficient degree to produce toxic changes. Yet in group IV, in which the disease was of longer duration, such results are not found. This in itself seems at first sight to contradict the conclusions for group III, but in an individual who has had the disease for more than two years there is probably a good deal of natural resistance to the process; it may be growing slowly and therefore not produce much general effect on the peripheral blood. On the other hand, the process may

be in a terminal stage and by reason of this prevent a normal reaction of the hematopoietic elements in the peripheral blood.

It is of interest that in this series of cases the most marked changes in the blood were seen in cases of inguinal adenopathy (group B). It is probable that in such cases there was associated involvement of the abdominal and pelvic retroperitoneal nodes, resulting in more widespread involvement than would be expected; consequently, more change in the cellular elements of the peripheral blood might have occurred. It is difficult to understand why individuals with generalized adenopathy (group D) should not present more changes in the cells of the blood, for as shown in table 2 this group has, on the average, leukocytes and individual cells in normal numbers. Apparently the extent of involvement of the process has but little effect on the changes in the blood.

Monocytosis did not occur in any of the groups, which is in accord with the conclusions of recent investigators in this subject. The individual cells have a greater tendency to be indented (shift to the right) than normal, but as this may occur in many other conditions it is without diagnostic significance.

Polymorphonuclear leukocytosis is not a constant finding but was present in this series in cases in which the disease had been present for more than one year and less than two years. The absence of polymorphonuclear leukocytosis in earlier cases would be contradictory evidence for the thesis that Hodgkin's disease has its origin in an infectious process.

Summary and Conclusions

The analysis of the findings in 40 cases of Hodgkin's disease revealed that: Leukocytosis of slight degree was present in cases in which the disease was of between one and two years' duration. Polymorphonuclear neutrophiles were slightly increased in the differential count in cases in which the disease was of six months' duration or longer. A slight relative decrease in the number of lymphocytes occurred in the same cases. The monocytes showed a greater tendency toward a shift to the right than occurs in normal individuals. Extensiveness of the disease apparently does not produce more marked changes in the blood. There is no specific change in the leukocyte picture which is diagnostic of Hodgkin's disease.

In the nine cases of lymphosarcoma, the average percentage of polymorphonuclear neutrophiles was slightly decreased and the average percentage of lymphocytes slightly increased as compared with the results in cases of Hodgkin's disease. The percentages of other leukocytes and the total leukocyte count were nearly the same as they were in cases of Hodgkin's disease.

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THE INTERRELATIONSHIP OF GASTROINTESTINAL AND RENAL DISEASE *

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CLINICALLY disease of the kidney and disease of the gastrointestinal tract are clearly differentiated in a majority of the cases. Frequently, however, the various types of renal disease give rise to symptoms referred mainly or even exclusively to the gastrointestinal tract. In a majority of these cases a careful examination will reveal the source of the disturbance. In some instances, however, severe gastrointestinal distress alone may result from pathological changes in the urinary tract which are not detected in a routine examination. It is with this group of cases that this paper is concerned. The digestive disturbances are purely functional and clear up entirely when the underlying renal abnormality is corrected.

An explanation of the reference of symptoms between these two systems may be sought in their anatomic, neurologic, and metabolic relationships. The anatomic relationship may be summarized by pointing out that the anterior surface of each kidney is in close apposition to important structures forming part of the gastrointestinal system: on the right the kidney is in close vicinity to the liver, the duodenum, and the hepatic flexure of the colon; while on the left the kidney is in contact with the stomach, spleen, pancreas and descending colon. The innervations of both the digestive and urinary tracts are similar in that they contain autonomic fibers of both vagal and sympathetic type which have passed for the most part through the celiac plexus. From a metabolic point of view both the digestive tract and the kidney possess excretory functions. A definite balance exists as to the proportion of certain substances which will be excreted in the stools or in the urine. In case of renal failure an added excretory function may be laid upon the digestive glands.

In all these interrelationships must lie the secret of the functional disturbances so frequently set up in one system as a result of a disease process localized in the other. Of the exact mechanisms involved we are still quite ignorant. From the clinician's point of view, however, the following notes upon the incidence of such referred symptoms may be of practical value.

Anatomically almost the entire anterior surface of both kidneys is in close relationship with various parts of the digestive apparatus. They are separated from it by a layer of fatty areolar tissue, and by the peritoneum which in places forms folds or ligaments which extend to neighboring organs. Traction on the duodenorenal and nephrocolic ligaments is believed to be an important factor in the production of gastric symptoms (Hinman, Longyear).

Both the kidneys and ureters and the gastrointestinal tract, including

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the liver, gall-bladder and pancreas, derive their nerve supply from almost the same sources: the vagus and the sympathetic fibers from the celiac plexus.

To a lesser extent pathological conditions in either system may affect the other through alterations in the chemical composition of the blood and body fluids which they may bring about. This is seen most strikingly in the digestive disturbances so common in uremia.

Hydronephrosis. Hydronephrosis from various causes is frequently associated with gastrointestinal symptoms. Renal symptoms may be slight or absent, and there may be no abnormality in the urine when tested.

The difficulty in differentiating renal and gall stone colic is well recognized. Forman calls attention to the following signs and symptoms which suggest a renal origin: there is reflex rigidity of the lumbar muscles; the pain is radiated caudad; bile does not appear in the urine; blood or pus may be present in the urine, although between attacks the urine may be normal; bimanual examination may elicit tenderness in the kidney area; and roentgen-ray may show evidence of renal disease, such as stone, stricture, hydronephrosis, etc.

Movable Kidney. Morrissey regards the production of gastrointestinal symptoms in movable kidney as the result of direct traction on the gastrointestinal tract. Traction, he believes, is exerted on the second portion of the duodenum through its areolar tissue connection with the right kidney. The lack of mesentery prevents it from moving forward, so that it is stretched and its lumen becomes diminished. Interference with the digestive current and secondary dilatation of the stomach follow; while at the same time, the bile ducts are elongated and narrowed, and the passage of bile through them is interfered with. On the left side similar disturbance of digestion may follow the pull of the kidney on the stomach and colon.

Nephrocoloptosis. Longyear believes that the kidney alone cannot exert sufficient traction on the gastrointestinal tract to produce symptoms, but that the combined ptosis of kidney and colon can initiate gastrointestinal symptoms. In the production of these symptoms the nephrocolic ligament plays an important part. Four factors, he states, are necessary for the occurrence of nephrocoloptosis, namely: (1) a weak or absent hepatocolic ligament, (2) a loose kidney attachment at its hilum and to Gerota's capsule, (3) a strong and short nephrocolic ligament, and (4) a prolapse of the cecum and ascending colon. Nephrocoloptosis occurs commonly on the right side but rarely on the left side; the reason being that on the right side the hepatocolic ligament, which helps to support the ascending colon, may be weak or absent, while on the left side the phrenocolic ligament, which supports the descending colon at the splenic flexure, is always present. Further, it is uniformly strong and dependable, and so prevents the downward displacement of the gut at this point. Fowler believes that ptosis of the adrenal gland is also a factor in producing this syndrome.

In nephrocoloptosis there is traction on the duodenum, causing angulation of the bowel and interference with the function of the biliary and pan-

creatic ducts. The symptoms are commonly gastrointestinal in character rather than renal. The patients complain of indigestion, distress after eating, gas eructations, nausea, constipation, flatulence, pain in both hypochondria which is either dull or colicky, and pain in the right lower quadrant. For treatment Longyear recommends an abdominal support, and also the surgical operation of nephrocolopexy which fixes both the kidney and colon.

Not all writers agree that ptosis of the kidney is always secondary to ptosis of the colon. According to Hinman, most authorities believe that the majority of surgical nephroptoses are not accompanied by enteroptosis, and that not all cases of visceroptosis are accompanied by nephroptosis.

Ureteral Stricture. Ureteral stricture is one of the diseases of the urinary tract which are most frequently associated with gastrointestinal disturbances. We owe to Hunner credit for demonstrating the relatively frequent occurrence of this condition.

Ureteral stricture may be of congenital or acquired origin. The acquired form which predominates is attributed to focal infection, infectious disease, or traumatism.

The symptomatology is variable. In one group of cases attention is directed at once to the urinary tract by attacks of ureteral colic. These are attributed by Watkins and Cumming to sudden occlusion of the ureter by edema of the strictured area.

In a much larger group the symptoms are so diverse and so predominantly gastrointestinal in character that without painstaking study the stricture may be overlooked. Thus in a series of 50 cases reported by Dabney severe digestive disturbances occurred in over 75 per cent, and pain referred to the right lower quadrant occurred in 34 per cent.

Pain is the most frequent symptom of ureteral obstruction. It varies in character from a constant dull nagging ache to a sharp violent paroxysmal pain. This may be present in the right lower quadrant, or it may be diffuse over the entire abdomen, and not referred to the urinary tract. Other symptoms frequently met with include indigestion, anorexia, nausea, vomiting, headache, flatulence, diarrhea, and rectal pain. Hunner emphasizes that careful inquiry will often elicit a history of occasional slight irritability of the bladder, or frequent micturition, particularly when nervous or excited, or at the menstrual period, or in association with a cold. Painful coitus may be complained of.

Urine analysis is not always helpful. Hunner found in 20 per cent of his cases a chronic pyelitis with characteristic abnormalities in the urine. In 50 per cent minor abnormalities were found: a few erythrocytes, a few leukocytes, albumin in varying amounts, or casts, or a combination of these elements. In 30 per cent the urine was normal.

Physical examination may reveal tenderness on bimanual palpation over the kidney region, or on pressure over the point where the ureter crosses the pelvic brim, approximately one and a half inches lateral to and below the umbilicus. This may elicit pain which radiates to the bladder. On vaginal

examination pressure over the ureters in the broad ligament above the bladder may cause tenderness or pain which may be recognized by the patients as identical with that with which they are familiar.

Difficulties often arise in the differentiation of chronic appendicitis from ureteral stricture. As Dabney has emphasized, both conditions are characterized by a chronic course, by a tendency to digestive disturbances and constipation, by pain in the right lower quadrant of the abdomen, and by the fact that exercise is not well borne. In both there is often tenderness in the right lower quadrant, and occasionally a slight elevation of the temperature and leukocyte count, while the urine may show no abnormality. Whenever there is a reasonable possibility of ureteral stricture a urologic examination should be carried out, including ureteral catheterization and a urogram.

Case Reports

The following case reports illustrate some instances of renal disease that presented essentially gastrointestinal symptoms.

Case 1. Renal Tuberculosis with Stricture of the Right Ureter. Miss M. M., aged 26, complained of loss of appetite, gas pains, excessive flatulence, bilious spells, dizziness, loss of strength, and inability to gain weight, all of which were several years in duration.

Physical examination showed an asthenic young white woman, 102 pounds in weight, 5 feet 5 inches in height, pulse 90, temperature 98, respiration 14, blood pressure systolic 105, diastolic 65, who was not acutely ill. The eyes reacted to light and to accommodation. The heart was not enlarged and the sounds were clear. The lungs were normal. The liver and spleen were not palpable. The descending colon was spastic, palpable and tender. There was vague abdominal distress in the entire lower abdomen which was not clearly localized. A pelvic examination was not made.

The blood count showed a moderate secondary anemia. The urine was quite normal, there was only an occasional leukocyte and an occasional epithelial cell present. The basal metabolic rate, Ewald test meal and stool examinations all were normal.

Roentgen-ray showed normal lung fields, dropped type heart, ptosis and spasticity of the colon.

The diagnosis at this time was: Undernutrition of 31 pounds, secondary anemia, visceroptosis, spastic colon. There was no evidence of tuberculosis and little reason to suspect it.

On a full diet she gained 12 pounds during the next two months, and the digestive symptoms subsided.

However in the third month she complained of polyuria and dysuria. The urine at this time contained large numbers of leukocytes and acid-fast bacilli which, on guinea pig inoculation, proved to be tubercle bacilli. The lungs again showed no evidence of tuberculosis on physical and roentgenoscopic examination. Cystoscopic examination by Drs. T. L. Howard, J. M. Lipscomb and J. E. Hartley revealed that the left kidney was normal and that the leukocytes and acid-fast bacilli came from the right kidney. A catheter encountered a stricture a short way up the right ureter. The kidney was subsequently removed by Drs. Howard, Lipscomb and Hartley and the patient made an uneventful recovery.

Comment. This patient probably had a renal tuberculosis at the time she presented herself for examination. However there were no external

manifestations of the disease. The symptoms she presented were essentially gastrointestinal, and the urine was entirely normal. When the focus of tuberculosis in the kidney broke through into the urine, the diagnosis became apparent.

Case 2. Stone in Left Ureter. Mr. M. D., aged 22 years, complained of attacks of indigestion which came on at irregular intervals over a period of several months. During these attacks he had severe pain in the left lower quadrant of the abdomen, he was nauseated, had a distaste for food, usually had a diarrhea. The attacks were completely relieved by bromides. Between attacks he felt well, but was very nervous and high strung. He had been examined in a large clinic, and prostatic massage had been advised.

Physical examination showed a well nourished young man, weighing 138 pounds, 5 feet 8 inches in height; pulse 78, respiration 14, temperature 98, blood pressure 115 systolic and 80 diastolic. The eyes reacted to light and to accommodation. The throat and mouth were normal. The heart and lungs were approximately normal. The liver and spleen were not palpable. The descending colon was spastic, palpable and tender. There was tenderness on the left side of the abdomen which seemed to correspond more or less with the descending colon. The reflexes were present, equal and exaggerated. The blood count, Ewald test meal and urine were normal. The urine contained no blood, no albumin, only an occasional leukocyte.

Roentgen-ray of the gastrointestinal tract showed a spasticity of the descending colon, otherwise it was normal.

At this time, a diagnosis of spastic colon was made. There are no symptoms referable to the urinary tract, no polyuria, no dysuria, no pain in lumbar region or the genitals.

Several months later the patient had a sharp attack of pain, more severe than any of the preceding attacks. The attack was located in the lumbar muscles as well as in the abdomen, and it radiated down the leg. The urine at this time contained large numbers of erythrocytes, and the roentgen-ray showed a small stone in the left ureter which had not been discovered in any of the previous examinations. The stone was removed by transureteral manipulation. The patient has been free from symptoms for two years.

The small ureteral stone was undoubtedly present at the time the patient presented himself for examination, though it did not at first elicit the characteristic symptoms commonly associated with that type of lesion. In this case, only the appearance of the ureteral colic led to a correct diagnosis.

Case 3. Chronic Pyelitis with Stricture of Left Ureter. Mr. H. C. complained of attacks of severe pain coming on after eating. The pains were located in the right upper quadrant of the abdomen in the region of the liver. The pain was sharp, paroxysmal, colicky, it spread to the entire abdomen, and was so severe that it required sedative medication for relief. These attacks had been coming on about once a week for two months. The attacks commonly came on about one half hour after eating. Between attacks he was free of pain, but felt tired and languid; he had no strength and had lost some weight. He was troubled with excessive gas, belching and flatulence.

Physical examination showed a white male of 140 pounds, 5 feet 6 inches in height. His pulse was 72, the temperature 97, the respiration 15, the systolic blood pressure 130, and the diastolic 67. He was not acutely ill at the time he was seen. The eyes reacted to light and to accommodation. The tonsils were enlarged but not infected. The heart and lungs were approximately normal. The abdomen did not relax well. There was marked tenderness in the right upper quadrant, particularly along the costal margin. The entire right side of the abdomen was spastic. There

was some tenderness over the cecum. The reflexes were present, equal and exaggerated.

Roentgen-ray of the stomach, intestines and gall-bladder showed all of them to be normal.

The blood count gave a leukocyte count of 18,400. The Ewald test meal was normal, and the urine was loaded with pus cells and colon bacilli, but was free from bile. The stool contained the normal bile pigments. Cystoscopic examination showed the left kidney and ureter to be normal; the pus came from the right kidney, and a stricture was encountered in the ureter.

Diagnosis: Pyelitis, right side, with stricture of ureter.

This patient was seen through the courtesy of Dr. Maurice Levy of Denver.

The diagnosis in this patient presented little difficulty because examination of the urine indicated at once an involvement of the renal system. The case is of interest because all the symptoms were gastrointestinal in character and suggested a gall stone colic. The patient never mentioned a single symptom referable to the urinary system, and it was only on subsequent interrogation that the patient recalled that years previously he had had trouble with his kidneys.

Summary

1. While renal disease and disease of the gastrointestinal tract can usually be differentiated clearly, in a small group of cases the symptoms are confusing and may lead to errors in diagnosis.

2. The renal and gastrointestinal systems are related anatomically through their juxtaposition and their ligamentous attachments, and neurologically through their common innervation.

3. The following renal disorders have been reported as being common sources of gastrointestinal symptoms: stricture of the ureter, hydronephrosis, movable kidney, pyelitis, stone.

4. In these conditions examination of the urine may reveal no definite abnormality and therefore be of no aid in diagnosis.

5. Physical examination may be helpful in eliciting characteristic pain or tenderness on palpation of the kidneys or the ureters where they cross the pelvic brim, or at their lower ends within the broad ligaments.

6. A definite diagnosis can usually be established by means of ureteral catheterization and urograms.

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FURTHER OBSERVATIONS ON THE CAROTID SINUS REFLEX *

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In previous communications [1, 2, 3] I reported the incidence and the degree of cardiac slowing induced by the carotid sinus reflex in a series of 345 cases. The cases were divided into five groups as follows: Group I, coronary artery disease with definite myocardial damage; Group II, hypertension and hypertensive heart disease; Group III, rheumatic heart disease; Group IV, individuals with cardiac symptoms but no demonstrable cardiac disease; Group V, general constitutional disease (non-cardiac).

It was shown that the order of frequency and degree of response were Groups I, II, III, V and IV—the first showing the highest frequency and degree of response and the last the lowest. Males showed a higher frequency and degree of response than females, and there was an increase in frequency of response with advancing age.

The present communication deals with an analysis of 426 additional cases, consisting of 243 males and 183 females. These were all ambulatory cases, most of whom had cardiovascular disease.

The grouping of this series was as follows: Group I, arteriosclerotic heart disease; Group II, hypertension and hypertensive heart disease; Group III, arteriosclerotic and hypertensive heart disease; Group IV, rheumatic heart disease; Group V, psychoneurotic heart disturbances; Group VI, heart disturbances or disease of various other causes; and, Group VII, cases without cardiovascular disease. This finer subdivision was adopted in order to see how the carotid sinus reflex exhibits itself in more precise types of disease.

As in the previous paper only the cardio-inhibitory part of the carotid sinus reflex is reported. The vasomotor depressor effect of the reflex, exhibited by fall in blood pressure, and the other reflex effects induced by the carotid sinus pressure were not studied.

Detailed Analysis of Cases in This Series

Group I consists of 113 cases, 96 males and 17 females. All showed clinical evidence of general arteriosclerosis and coronary sclerosis of various degrees. In the majority of cases the electrocardiogram corroborated the presence of myocardial involvement. Many cases also had aortic sclerosis. Besides coronary disease, three cases had chronic bronchitis and emphysema, one Menier's syndrome, one congenital patent ductus arteriosus, three neurocirculatory asthenia, two diabetes mellitus, six obesity, one pulmonary tuberculosis, and three chronic cholecystitis and cholelithiasis.

* Received for publication December 14, 1935.

In 10 cases there was a history of recent or past coronary occlusion, which in one instance was followed by pulmonary embolism.

Group II consists of 45 cases, 14 males and 31 females. Although all showed more or less cardiac hypertrophy secondary to hypertension, none had gross evidence of insufficiency of the coronary circulation. In three cases the hypertension was of nephritic origin. In the rest it was of the so-called essential type. Fourteen cases showed marked obesity, six cases had definite psychoneuroses, two had chronic arthritis, one psoriasis, three cholecystitis and cholelithiasis, and one early multiple sclerosis.

Group III consists of 89 cases, 50 males and 39 females. All gave a history of hypertension and showed more or less hypertension at the time of the examination. All showed evidence of more or less general arteriosclerosis and coronary sclerosis. In addition, two had evidence of nephrosclerosis with early renal insufficiency. All had evidence of aortic sclerosis with more or less marked dilatation. Twelve cases showed considerable obesity; six gave a history of past coronary occlusion; four cases were diabetic; three showed psychoneurotic symptoms and three showed symptoms attributable to the menopause.

Group IV consists of 43 cases, 19 males and 24 females with chronic rheumatic heart disease. Fifteen showed mitral stenosis, one with auricular fibrillation; 16 had mitral insufficiency and mitral stenosis, four of whom had auricular fibrillation; two had mitral stenosis, mitral insufficiency and aortic insufficiency; three aortic insufficiency and stenosis; one aortic stenosis and mitral stenosis; three aortic insufficiency; three had mitral insufficiency. In addition two had hypertension, one chronic bronchitis, and one showed evidence of hyperthyroidism.

Group V consists of 23 cases, 10 males and 13 females with various cardiac manifestations of psychoneurotic origin. Care was taken to exclude from this group definite organic cardiac disease. All symptoms referable to the heart were entirely subjective. If objective findings were present, such as murmurs, various tachycardias and arrhythmias, they could invariably be considered to be functional in type.

Group VI consists of 52 cases, 26 males and 26 females. Some presented abnormal cardiac signs and symptoms of such character that the diagnosis of heart disease could not be made with certainty. Others had distinct heart disease of unknown etiology. Still others had cardiovascular disease of known etiology, but because they were relatively few in number no separate groups were made of them. Thus there were six cases of syphilitic aortic disease with reactive cardiac changes; six with thyrotoxic heart disease; two with congenital heart disease; one of chronic myelogenous leukemia with suspicious cardiac involvement; one secondary to marked chronic pulmonary lesions. Some cases might have been classed as neurocirculatory asthenia, but there was evidence suggesting early cardiovascular disease of arteriosclerotic origin.

Group VII consists of 61 cases, 28 males and 33 females. It includes cases of obesity, neurasthenia, menopause, gastric and duodenal ulcers,

anemias, diabetes, Hodgkin's disease, and so on. None showed clinical evidence of cardiovascular disease, although in a few, premature contractions or other cardiac abnormalities were observed, which could be attributed to reflex disturbances.

Cardiac Response to the Carotid Sinus Reflex

In a previous report [1] a separate analysis was made of the reflex cardiac response to right and left carotid sinus pressure, and to combined right and left pressure. Some individuals exhibited only a right pressure response, others a left, but most showed a bilateral response. The degree of response varied for the two sides in many individuals.

In this series, in order to simplify the results, only the maximum response was used to classify each case. This, as before, was obtained on right or left carotid sinus pressure or equally on both sides.

Table I

Response to Carotid Sinus Pressure among Males and Females

Groups	Total No. Cases		Total Not Responding		Total Responding and Percentage Response			
	Males	Females	Males	Females	Males		Females	
					No.	%	No.	%
I	96	17	18	4	78	81.2	13	76.5
II	14	31	2	7	12	85.7	24	77.4
III	50	39	8	13	42	84.	26	66.6
IV	19	24	4	10	15	78.9	14	58.3
V	10	13	4	8	6	60.	5	38.4
VI	26	26	8	13	18	69.2	13	50.
VII	28	33	6	12	22	78.5	21	66.6
Total	243	183	50	67	193	79.4	116	63.3

Group I—Arteriosclerotic heart disease
Group II—Hypertensive heart disease
Group III—Arteriosclerotic and hypertensive heart disease
Group IV—Rheumatic heart disease
Group V—Psychoneurotic heart disease
Group VI—Other forms of heart disturbances and disease
Group VII—General constitutional disease (non-cardiac)

Table 1 and figure 1 represent the response of this series of 426 cases. An analysis of the figures shows that the greatest frequency of response is in the hypertensive and in the arteriosclerotic and hypertensive groups. Rheumatic heart disease occurs next in frequency as does the non-cardiac group. The least response is seen in psychoneurotic heart disturbances and in the miscellaneous group of heart abnormalities. The latter shows a somewhat higher frequency of response than the psychoneurotic group. In all groups, females showed a definitely lower frequency of response than males.

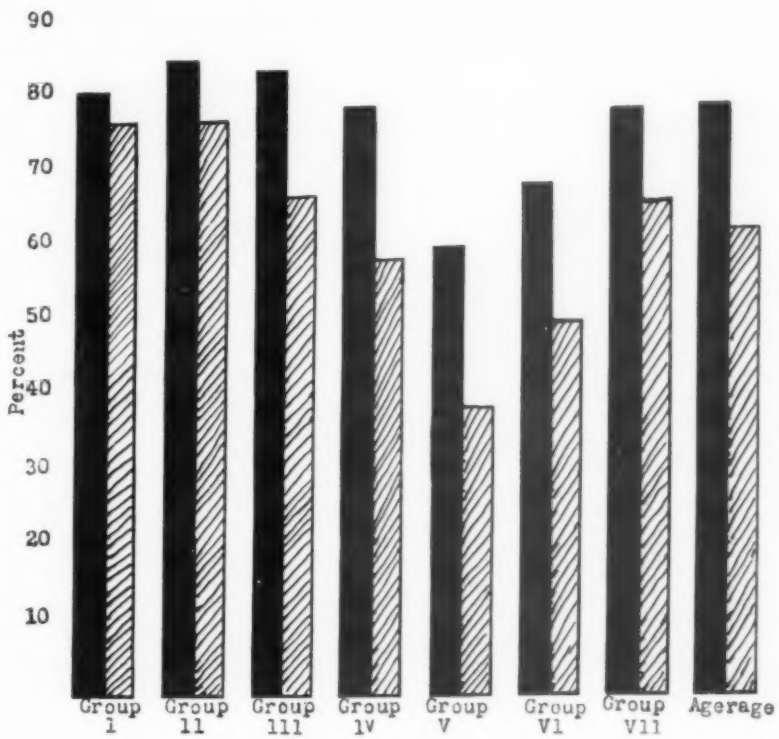

FIG. 1. Percentage response to vagal stimulation. Black column represents males; light column represents females. Ordinates represent percentage response; abscissae represent disease groups.

TABLE II

Degree of Slowing in the Various Groups

Groups	+				++				+++				++++			
	Males		Females		Males		Females		Males		Females		Males		Females	
	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
I	11	14.1	4	30.8	16	20.5	3	21.3	22	28.2	2	15.3	29	37.2	4	30.8
II	5	41.7	9	37.5	6	50.	6	25.	1	8.3	5	20.8	—	—	4	17.5
III	10	23.8	8	30.8	13	30.9	9	34.6	8	19.1	4	15.3	11	26.2	5	19.3
IV	4	26.6	7	50.	4	26.6	4	28.5	4	26.6	3	21.5	3	20.	—	—
V	—	—	2	40.	1	16.6	2	40.	4	66.6	—	—	1	16.6	1	20.
VI	—	—	1	7.6	9	50.	7	53.8	6	33.3	4	30.7	3	16.7	1	7.6
VII	6	30.0	6	28.5	6	30.0	10	47.6	5	25.0	4	19.	3	15.0	1	4.9
Total	36	18.8	37	31.9	55	28.8	41	35.4	50	26.2	22	18.9	50	26.2	16	13.8

\+ Slowing less than 25% of the original rate
++ 25% to 50%
+++ 50% to short stoppage of heart
++++ Where the heart stopped for more than two seconds.

Group I—Arteriosclerotic heart disease
Group II—Hypertensive heart disease
Group III—Arteriosclerotic and hypertensive heart disease
Group IV—Rheumatic heart disease
Group V—Psychoneurotic heart disease
Group VI—Other forms of heart disturbances and disease
Group VII—General constitutional disturbances (non-cardiac)

Degree of Slowing. In the previous report, slowing of the heart under the carotid sinus reflex was divided into three degrees—those showing less than 25 per cent slowing as compared to original heart rate; those more than 25 per cent; and those where the heart stopped for at least two seconds. In

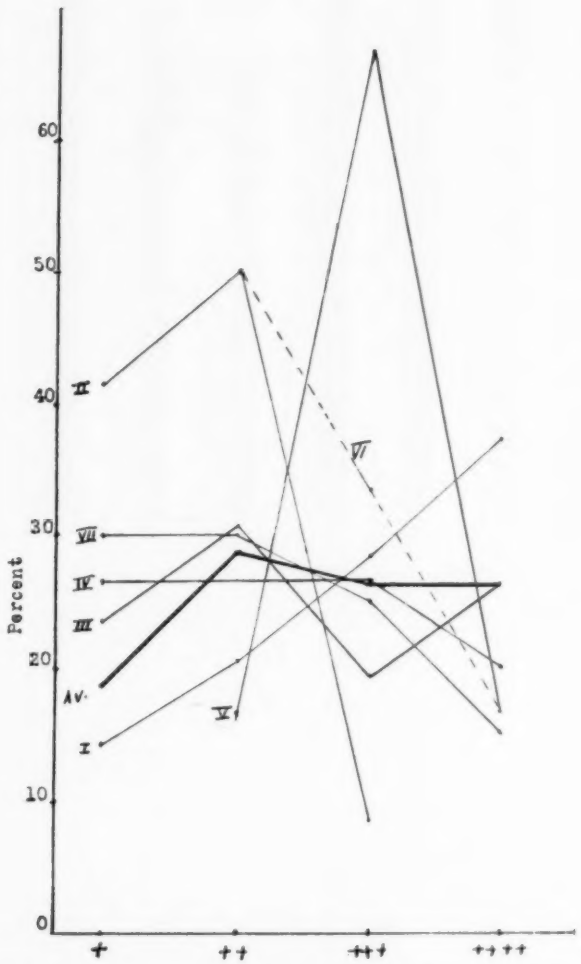

FIG. 2. Degree of slowing among males. + Slowing less than 25 per cent of the original rate; ++ Twenty-five to 50 per cent; +++ Fifty per cent to short stoppage of heart; ++++ Where the heart stopped for more than two seconds. Disease groups are represented by Roman numbers. Ordinates represent percentage response in the various groups; abscissae represent the degree of response.

this series the degree of slowing was divided into four groups. Those showing less than 25 per cent slowing were designated as one plus; those showing 25 per cent to 50 per cent slowing as two plus; those showing 50 per cent slowing to temporary stoppage of the heart as three plus; and those where the heart stopped for more than two seconds as four plus. Table 2

and figures 2 and 3 show the degree of response of the various groups among males and females respectively.

It will be seen that, with few exceptions, the tendency is for a greater percentage of cases to show the highest degree of slowing in the arteriosclerotic group. In the hypertensive group this tendency appears to be in the opposite direction. It is also interesting to note that adding hypertension

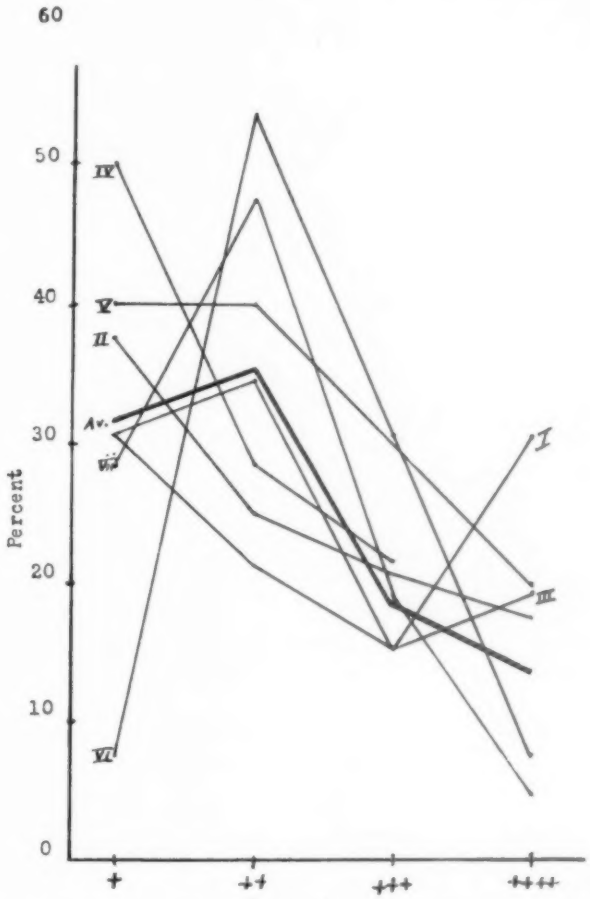

FIG. 3. Degree of slowing among females. + Slowing less than 25 per cent of the original rate; ++ Twenty-five to 50 per cent; +++ Fifty per cent to short stoppage of heart; ++++ Where the heart stopped for more than two minutes. Disease groups are represented by Roman numbers. Ordinates represent percentage response in the various groups; abscissae represent the degree of response.

to arteriosclerosis has a tendency to lessen the degree of slowing. All other groups likewise show a tendency toward a lesser degree of slowing except in the psychoneurotic group. In this group, however, no conclusions may be drawn because of too small a number of cases.

There is a definite tendency for females to show a lesser degree of slowing. In cases with 4 plus response, females invariably showed a shorter

stoppage of the heart than males. In most of the females the stoppage was for no more than two seconds and the average was about 2.5 seconds. Most of the males, on the other hand, showed a stoppage of more than three seconds and the average was about four seconds. The longest stoppage occurred in severe forms of arteriosclerotic heart disease where in a few

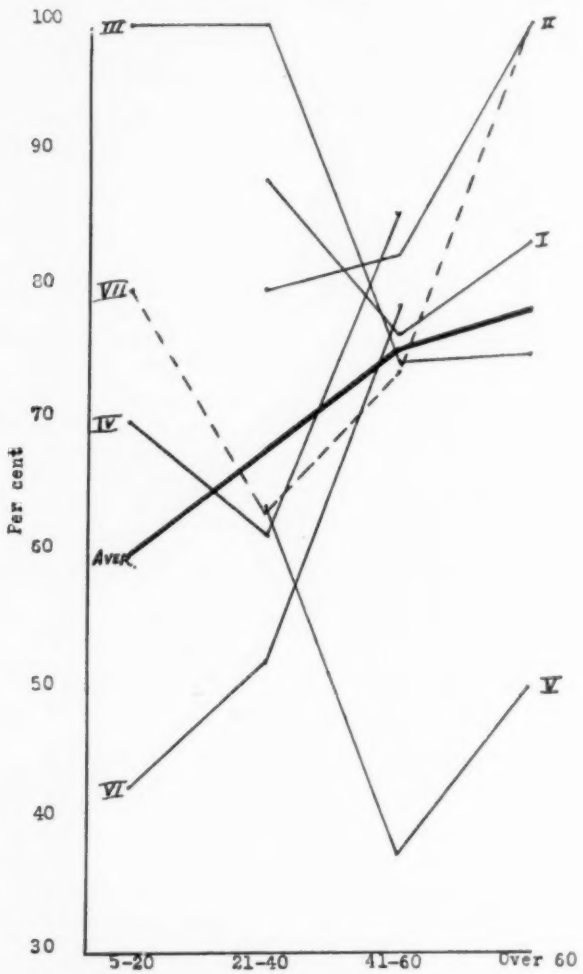

FIG. 4. Percentage response of the cardio-inhibitory carotid sinus reflex at given ages for both sexes. Ordinates represent percentage response; abscissae represent age groups. Disease groups are represented by Roman numbers.

cases the heart stopped for 5 to 14 seconds. In the non-cardiac group, if the heart stopped it was never for more than two seconds, and that was produced only by strong pressure.

Response at Various Ages. Table 3 and figure 4 are an analysis of the response at various age groups in this series. Although the first age group is marked 5 to 20 years of age, there were only two cases less than 10 years

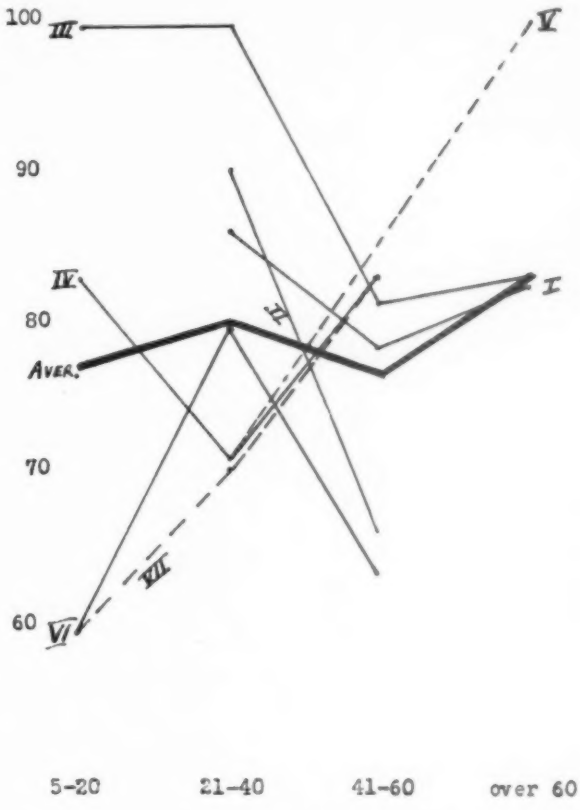

FIG. 5. Percentage response of the cardio-inhibitory carotid sinus reflex at given ages for males. Ordinates represent percentage response; abscissae represent age groups. Disease groups are represented by Roman numbers.

TABLE III

The Cardio-Inhibitory Carotid Sinus Reflex at Various Ages in the Various Groups

Males and Females

Groups	Ages 5–20 yrs.			Ages 21–40 yrs.			Ages 41–60 yrs.			Ages over 60 yrs.		
	Resp.	Not Resp.	% Resp.	Resp.	Not Resp.	% Resp.	Resp.	Not Resp.	% Resp.	Resp.	Not Resp.	% Resp.
I	0	0	0.0	15	2	88.2	46	14	76.6	30	6	83.5
II	0	0	0.0	16	4	80.0	19	4	82.6	1	0	100.0
III	1	0	100.0	5	0	100.0	41	14	74.5	21	7	75.0
IV	7	3	70.0	16	10	61.5	6	1	85.7	0	0	0.0
V	0	2	0.0	7	4	63.6	3	5	37.5	1	1	50.0
VI	3	4	42.8	13	12	52.0	15	4	78.9	0	1	0.0
VII	4	1	80.0	19	11	63.3	17	6	73.9	1	0	100.0
Average	15	10	60.0	91	43	67.9	147	48	75.4	54	15	78.1

Disease groups are the same as in tables 1 and 2.

of age, and three others less than 15 years. All others were near to or actually 20 years old.

With the exception of Groups III and V there is a definite increase in

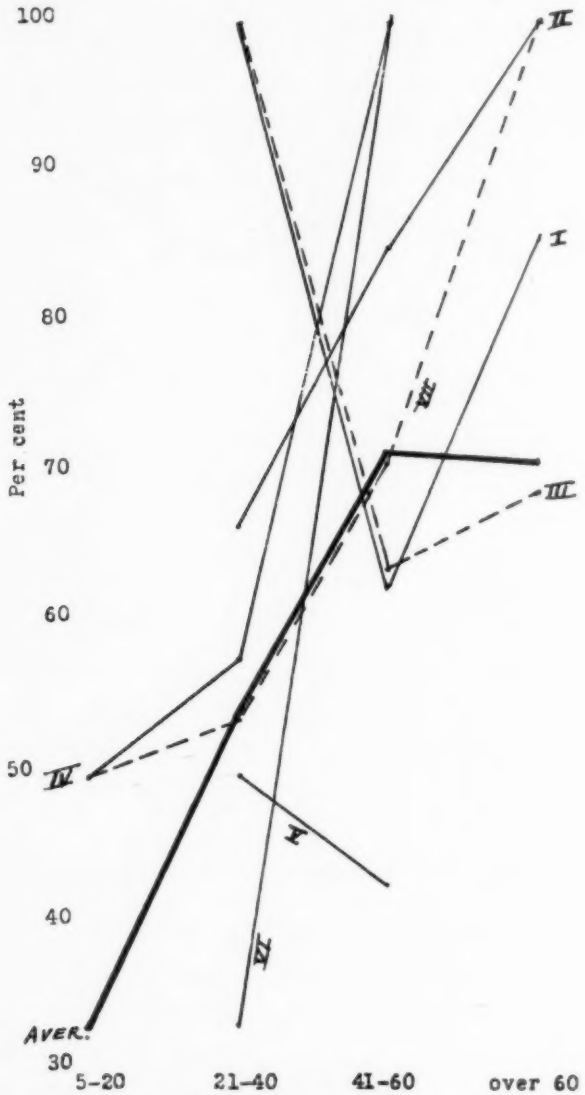

FIG. 6. Percentage response of the cardio-inhibitory carotid sinus reflex at given ages for females. Ordinates represent percentage response; abscissae represent age groups. Disease groups are represented by Roman numbers.

the incidence of response with advancing age. In Group V the total number of cases was too small to permit the drawing of conclusions. In Group III the number of cases in the early age groups is also too small for conclusions. The findings, however, seem to point to the fact that the presence of arterio-

sclerosis and hypertension even early in life will increase the incidence of the cardio-inhibitory response to carotid sinus pressure.

A separate analysis was made of the male and female age incidence of response. Table 4 and figure 5 show the male response, and table 5 and figure 6 the female response.

TABLE IV

The Cardio-Inhibitory Carotid Sinus Reflex at Various Ages in the Various Groups

Males

Groups	Ages 5–20 yrs.			Ages 21–40 yrs.			Ages 41–60 yrs.			Ages over 61 yrs.		
	Resp.	Not Resp.	% Resp.	Resp.	Not Resp.	% Resp.	Resp.	Not Resp.	% Resp.	Resp.	Not Resp.	% Resp.
I	0	0	0.0	13	2	86.6	41	11	78.8	24	5	82.7
II	0	0	0.0	10	1	90.9	2	1	66.6	0	0	0.0
III	1	0	100.0	4	0	100.0	27	6	81.8	10	2	83.3
IV	5	1	83.3	5	2	71.4	5	1	83.3	0	0	0.0
V	0	1	0.0	5	2	71.4	0	1	0.0	1	0	100.0
VI	3	2	60.0	8	2	80.0	7	4	63.6	0	0	0.0
VII	3	2	60.0	12	5	70.5	5	1	83.3	0	0	0.0
Average	12	6	77.7	57	14	80.2	87	26	77.0	35	7	83.3

TABLE V

The Cardio-Inhibitory Carotid Sinus Reflex at Various Ages in the Various Groups

Females

Groups	Ages 5–20 yrs.			Ages 21–40 yrs.			Ages 41–60 yrs.			Ages over 61 yrs.		
	Resp.	Not Resp.	% Resp.	Resp.	Not Resp.	% Resp.	Resp.	Not Resp.	% Resp.	Resp.	Not Resp.	% Resp.
I	0	0	0.0	2	0	100.0	5	3	62.5	6	1	85.7
II	0	0	0.0	6	3	66.6	17	3	85.0	1	0	100.0
III	0	0	0.0	1	0	100.0	14	8	63.6	11	5	68.7
IV	2	2	50.0	11	8	57.8	1	0	100.0	0	0	0.0
V	0	1	0.0	2	2	50.0	3	4	42.8	0	1	0.0
VI	0	2	0.0	5	10	33.3	8	0	100.0	0	1	0.0
VII	1	1	50.0	7	6	53.8	12	5	70.5	1	0	100.0
Average	3	6	33.3	34	29	54.0	60	24	71.4	19	8	70.5

It will be seen that males have a tendency to show a greater incidence of response earlier in life than do females. Females show a more regularly progressive increase in response with advancing age. In males, on the other hand, the type of disease seems to be more important as a determining factor than the age. The greatest *degree* of response occurred in later life, in each sex.

Discussion

It was well established by many investigators that stimulation of the carotid sinus induces two major independent reflexes—slowing of the heart and fall in blood pressure. Heymans [5] found three other reflexes—a direct cerebral vascular reflex; changes in adrenalin secretion; and changes in respiration. That each one of these reflexes is independent of the others has likewise been well established. Thus Hering [6] found that vagotomy and atropinization abolished the cardio-inhibitory reflex, while the fall in blood pressure could still be induced by carotid sinus pressure. Koch,[7] Heymans,[5] and various other observers have likewise demonstrated this point repeatedly.

The investigation reported in this paper as well as in the previous ones deals only with the cardio-inhibitory part of the carotid sinus reflex. Although slowing of the heart thus induced reflexly may to some extent be due to inhibition of the cardio-accelerator nerves as shown by Raginers,[8] and Bronk, Ferguson and Solandt,[9] it is dependent predominantly upon reflex vagal stimulation, as evidenced by the effects of vagotomy and atropinization mentioned before.[6] The cardio-inhibitory carotid sinus reflex response may then be considered to be an index of sensitivity of the vagus to reflex stimulation. This sensitivity varies in frequency and in degree. In normal individuals Sander [10] found a fairly high incidence of response. The degree of response, in normal persons, however, is comparatively low.

Various forms of local and constitutional disease increase the incidence and degree of the vagal response. Hering,[6] Koch,[7] and Heymans [5] attributed an increased response in some individuals to sclerosis of the carotid artery in the region of the sinus. This seems to have been disproved by Keele [11] who found no relationship between fall in blood pressure induced by carotid sinus pressure and localized sclerosis, in a series of 55 autopsy cases. Braun and Samet [12] found marked response associated with coronary disease. Danielopolu and Missirlin [13] found an exaggerated reaction in chronic myocardial disease. Wenckebach [14] likewise found it in association with cardiac disease. Various authors such as Koch, Hering, Heymans and others found that drugs, as digitalis, morphine, calcium chloride and chloroform, increased the carotid sinus reflex response.

The results reported in this paper and in the previous ones substantiate the fact that the incidence and degree of response are greatly enhanced by arteriosclerotic heart disease, where the greatest degree of response is obtained. Other disease states, however, are associated with the reflex in greater or less incidence. Sex and age play a rôle in determining the response, being greater among males and in advancing age. Various types of disease likewise appear to have some influence. Patients with neurocirculatory disturbances and no real organic disease appear to present the least incidence and degree of response. Hypertension, although increasing the incidence, decreases the degree of response. One interesting observa-

tion in this paper is that besides the greater male incidence of increase in the carotid sinus reflex, the reflex seems to occur in greater number and degree earlier in life among males than among females.

All these factors point to a constitutional vagotonic tendency which is influenced by various factors. Disturbances in internal secretions undoubtedly play a part in influencing the reflex, as evidenced by the variations in the sex incidences of response, in the same disease states. The nervous state of the individual is another factor as evidenced by the diminished response in neurocirculatory asthenia. The gradual increase in response with advancing age may be due to a gradual and progressive sensitization of the vagal center by toxic states. The increase in the *incidence* of response in hypertension may be explainable on the basis of sensitization of the receptor nerve endings in the carotid sinus by increased intra-carotid pressure. This also partly explains the diminished response in neurocirculatory asthenia where the blood pressure is usually low. The persistent stimulation in hypertension appears to induce a moderate fatigue of the receptors, diminishing the *degree* of response.

Summary

In previous reports an analysis was made of the slowing of the heart induced by the carotid sinus reflex, in a series of 345 cases. This paper deals with a similar analysis of 426 additional cases. This series was divided into seven groups: (1) arteriosclerotic heart disease; (2) hypertension and hypertensive heart disease; (3) arteriosclerotic and hypertensive heart disease; (4) rheumatic heart disease; (5) psychoneurotic heart disease; (6) other forms of heart disease or disturbances; and (7) general constitutional disturbances (non-cardiac).

It was found that the greatest frequency and degree of slowing occur in arteriosclerotic and hypertensive heart disease. Rheumatic heart disease comes next and general constitutional disease follows. The psychoneurotic and the miscellaneous groups of heart disease showed the least response. Hypertension seems to increase the frequency but to diminish the degree of the carotid sinus reflex response. The incidence and degree of response are greater among males than females and increase with advancing age. Males show the response in greater degree and incidence earlier in life than females.

The cardio-inhibitory reflex appears to depend on a constitutional vagotonic tendency which is more marked among males and develops with advancing age. General toxic or irritative states, endocrine factors, intra-carotid blood pressure, and local disease or disturbances in the heart itself, seem to play a part in sensitizing the reflex.

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PHOSPHATASE CONTENT OF HUMAN SERUM IN PULMONARY TUBERCULOSIS FOLLOWING THE ADMINISTRATION OF VITAMIN D*

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Phosphatase is an organic catalyst capable of either synthesizing or hydrolyzing any mono-ester of phosphoric acid. It was first discovered in rice and wheat bran by Suzuki, Yoshimura and Takaishi [1] in 1907. (For a full review of the literature see Kay.[2]) It is present in large quantities in the intestinal mucosa, kidney and bone. Smaller quantities are found in practically all other organs and secretions. Fetal bone and the bone of young animals are richest in the enzyme, but the content diminishes as maturity is reached. The optimum pH in vitro is around 9—it is activated by Mg (Erdtman [3]) and inhibited by pepsin, iso-leucine and glycine (Bakwin and O. Bodansky [4]). Robison and Soames [5] have shown its importance as a local factor in bone formation and have demonstrated the precipitation of calcium phosphate in bone slices, from a rachitic animal, immersed in calcium glycerophosphate. We have recently shown,[6] supporting the work of other investigators,[7, 8] that in the rat the phosphatase content of serum and kidney is reduced following massive doses of viosterol and that it is greatly increased in the small intestine. Changes in the bone were found to be variable.

Method

Determinations of serum phosphatase were made upon normal human beings and upon tuberculous individuals before and after the administration of viosterol, according to the method of Bodansky.[9, 10] Blood samples were obtained in each case within an hour after the noon meal. The blood was centrifuged and all determinations were made immediately. The unit of phosphatase is equivalent to 1 mg. of phosphorus liberated from a glycerophosphate substrate in one hour at pH 8.6 and at 37° C. The calcium determinations were made simultaneously from the same specimen of serum.

Experimental

Blood Serum Phosphatase in Normal Humans. Serum phosphatase determinations were made on 19 normal human beings (table 1). The lowest figure was 1.68 units and the highest 4.96 units per 100 c.c., the average being 3.31 units. In one case, not recorded in the table, the serum phosphorus and substrate phosphorus were respectively 4.49 and 14.14,

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yielding 9.65 units of phosphatase. There was no apparent reason for this. Bakwin and Bodansky [4] give the normal range as being between 1.5 and 4.5 units per 100 c.c.

TABLE I

Serum Phosphatase of Normal Human Beings

Case Number	Serum Phosphorus Mg. per 100 c.c.	Substrate Phosphorus Mg. per 100 c.c.	Units Phosphatase (By Difference)
1	3.40	6.82	3.42
2	4.21	5.89	1.68
3	3.53	8.27	4.74
4	3.46	6.47	3.01
5	3.42	7.48	4.06
6	3.78	7.92	3.14
7	2.48	5.32	2.84
8	3.95	7.35	3.40
9	3.57	8.53	4.96
10	3.80	7.57	3.77
11	2.58	6.47	3.89
12	3.82	6.42	2.60
13	3.95	6.95	3.00
14	3.10	6.73	3.63
15	3.57	5.66	2.09
16	3.42	5.94	2.52
17	3.38	5.33	1.95
18	3.27	6.29	3.02
19	2.48	6.73	4.25
Average	3.43	6.74	3.31

Blood Serum Phosphatase in Pulmonary Tuberculosis. The phosphatase of the serum of 32 cases of pulmonary tuberculosis ranged from 1.36 to 4.45 units, with exception of one case which was 6.38 units (table 2). In three additional cases, all of which were moribund, the phosphatase content averaged 12.06 units per 100 c.c. (table 3).

In any stage of pulmonary tuberculosis the phosphatase activity is not greatly disturbed, and the values fall within normal limits. The reason for the elevation in the moribund cases is not known. The three cases mentioned above were in an extreme state of emaciation and cachexia. It is not to be inferred, however, that an elevated phosphatase content is a sign of impending death, since other patients in this series have since died, and bloods obtained post mortem on still others were quite normal for phosphatase.

Blood Serum Phosphatase in Tuberculous Patients Following Administration of Vitamin D. Twenty-four tuberculous patients were given viosterol, 10,000 X,* 1 c.c. daily for 10 days. The calcium, phosphorus and phosphatase content of the sera was determined before and after administration. No attempt was made to secure a great elevation of serum calcium. If the patients became toxic before taking the full dosage of 10 c.c. the drug was discontinued. The average serum calcium before the administration

* 10,000 times average cod liver oil, 1,000,000 I.U. per gram; kindly supplied by Mead Johnson and Company, Evansville, Indiana.

TABLE II

Serum Phosphatase in Pulmonary Tuberculosis

Case Number	Serum Phosphorus Mg. per 100 c.c.	Substrate Phosphorus Mg. per 100 c.c.	Units Phosphatase (By Difference)
1	3.94	7.57	3.63
2	3.99	8.44	4.45
3	2.60	6.29	3.69
4	3.19	6.20	3.01
5	2.70	6.68	3.98
6	3.23	6.41	3.18
7	3.31	7.39	4.08
8	2.77	6.11	3.34
9	2.77	4.79	2.02
10	2.37	4.18	1.81
11	3.80	5.95	2.15
12	3.14	4.53	1.39
13	3.02	6.33	3.21
14	2.85	5.10	2.25
15	3.29	5.67	2.38
16	2.56	4.66	2.10
17	3.86	7.08	3.22
18	3.78	10.16	6.38
19	2.36	5.98	3.62
20	3.08	6.16	3.08
21	2.81	5.76	2.95
22	3.50	6.51	3.01
23	3.43	5.32	1.89
24	3.43	5.12	1.69
25	3.48	5.94	2.46
26	3.27	5.63	1.36
27	3.65	6.44	2.79
28	3.27	7.34	4.07
29	3.88	7.26	3.38
30	2.94	5.01	2.07
31	3.02	5.40	2.38
32	3.63	6.55	2.92
Average	3.22	6.17	2.95

TABLE III

Serum Phosphatase in Three Moribund Cases of Pulmonary Tuberculosis

Case Number	Serum Phosphorus Mg. per 100 c.c.	Substrate Phosphorus Mg. per 100 c.c.	Units Phosphatase (By Difference)
1	4.26	17.74	13.48
2	3.60	15.40	11.80
3	4.11	15.00	10.89
Average	3.99	16.05	12.06

of viosterol was 11.8 mg. per 100 c.c. of blood serum. Following administration of viosterol 24 blood sera averaged 14.2 mg. per 100 c.c. In the same patients the phosphatase content of the blood serum before administration of viosterol averaged 3.29 units per 100 c.c. and 3.06 units per 100 c.c. following administration of viosterol. This shows a slight decrease in

TABLE IV

Twenty-Four Cases of Pulmonary Tuberculosis before and after the Administration of Viosterol, 10,000 X

Case Number	Serum Calcium (Mg. per 100 c.c. of Blood Serum)		Serum Phosphatase Units per 100 c.c. of Blood Serum	
	Before Viosterol	After Viosterol	Before Viosterol	After Viosterol
1	11.5	12.5	2.45	2.26
2	11.7	11.3	3.03	3.73
3	11.5	13.0	4.38	4.43
4	11.6	12.5	4.52	4.41
5	11.5	13.3	3.11	2.95
6	12.0	12.9	2.53	1.79
7	11.1	15.2	3.76	3.04
8	12.1	16.4	3.99	5.16
9	11.0	13.5	2.63	2.85
10	11.8	18.6	2.66	2.39
11	10.5	14.4	3.96	4.39
12	11.8	17.2	3.06	2.02
13	12.8	15.6	4.36	2.74
14	12.1	15.6	3.23	1.26
15	10.8	13.8	2.64	3.13
16	9.9	14.3	2.97	3.09
17	10.8	13.3	3.90	3.47
18	12.2	13.1	2.23	3.92
19	12.7	14.4	3.04	3.00
20	13.0	13.3	2.57	2.64
21	12.9	13.3	2.62	2.24
22	12.6	16.3	3.53	1.64
23	12.7	13.5	4.61	3.45
24	12.4	14.2	3.33	3.43
Average	11.8	14.2	3.29	3.06

the phosphatase content. A detailed analysis shows that a decrease of phosphatase occurred in 14 cases, whereas in 10 there was an increase of phosphatase in the blood serum. However, in 11 patients who had an elevation of the serum calcium over 14.0 mg. per 100 c.c., seven showed a decrease in the phosphatase content, while four showed an increase.

SUMMARY

1. The phosphatase content of a normal human serum was found to average 3.31 units in a series of 19 cases.

2. In 32 cases of pulmonary tuberculosis, all stages, the phosphatase content averaged 2.95 units.

3. Administration of viosterol, 10,000 X, in dosage resulting in hypercalcemia, caused a slight reduction of serum phosphatase in blood serum. Fourteen cases of pulmonary tuberculosis showed a decrease while ten showed an increase. Seven of the 11 whose serum calcium was 14.0 mg. or over showed a decrease in serum phosphatase content.

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DIAGNOSIS OF DISSECTING ANEURYSM OF THE AORTA *

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Although more than 400 cases of dissecting aneurysm have been reported, only 11 have been correctly diagnosed during life. Shennan,[1] in an extensive review of the literature up to 1933, accepts six cases.[2] He does not accept the cases of Finny (1885), Prescott (1897), Mager (1908), and Heller (1904). Since Shennan's review, five more cases [3] have been diagnosed during life. Hamman [4] and Gatewood [5] have each diagnosed a case after death but before the necropsy findings were known.

The purpose of this paper is to report two additional cases diagnosed during life and to outline briefly the clinical and pathologic features of this condition. It is hoped that our summary of the salient characteristics of dissecting aortic aneurysm will result in its more frequent recognition during life.

Case Reports

Case 1. J. N. S., a white male, aged 50, entered Multnomah County Hospital on Oct. 18, 1934, complaining of pain in the abdomen and chest, with vomiting. The patient was well until 2:30 p.m., of the day of entrance when, following a heavy meal, he was suddenly seized with a steady, sharp pain in the epigastrium and lower chest, radiating to the right and left sides of the abdomen, to the back of the chest and into the left flank. The pain was diffuse and poorly localized. Lying flat on the floor was the only position which afforded relief. There was no vomiting at this time but definite nausea. After a short time the pain gradually subsided but soon recurred with greater intensity and remained steady with no cramp-like exacerbations. There was some shortness of breath associated with the pain, and the patient felt as though his heart was "about to jump out of his body." There was also some dizziness and spots before the eyes. Vomiting first occurred at 7:00 p.m. and was repeated six times in the next four hours.

From the past history it was learned that the patient contracted syphilis about 1917 but was treated for only a short time. In August 1932, he entered Multnomah County Hospital where a diagnosis of syphilitic meningitis and hypertensive cardiovascular renal disease was made. The Kolmer and Kahn were 4 plus. Following his discharge he was treated in the Outpatient Syphilis Clinic. In September 1933, he reëntered the hospital with a diagnosis of basilar subarachnoid hemorrhage on the basis of hypertensive disease or syphilitic vascular changes. The blood pressure at this time was 190 systolic and 118 diastolic. He was discharged Dec. 10, 1933 and was in fairly good health until the onset of the present illness.

Physical examination on Oct. 19, 1934 revealed a well developed, well nourished, middle-aged male, obviously in pain, preferring to lie on his right side but occasionally turning from side to side and very apprehensive. His face was flushed but not cyanotic. There was no dyspnea. The blood pressure was 182 systolic and 88 diastolic and equal in both arms. The pulse was 98 and regular; the temperature,

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100° F. (37.8° C.). Vigorous systolic pulsation was visible in the carotid vessels and palpable in the suprasternal notch and over the left subclavian artery. The peripheral vessels were tortuous and thickened with some sclerotic beading. The heart was enlarged, particularly to the left, and the pulsations were strong. The impact of the aortic valve closure was palpable. Percussion showed upper sternal dullness of considerable degree. The heart was aortic in configuration with widening of the base. The heart tones were clear and sharp, and there was a long blowing systolic murmur over the mitral area. The aortic second sound was markedly accentuated but not metallic in character. There was no murmur over the aorta posteriorly. The lungs showed no evidence of congestion. There was moderate resistance over the upper abdomen particularly on the left side, but no definite area of localized tenderness. Excursion of the costal margin with deep inspiration was normal. There were no changes in the extremities; the peripheral vessels showed equal normal pulsation.

The diagnosis on admission was coronary thrombosis or some form of acute abdominal disease. Because of the presence of long standing hypertension on the basis of hypertensive cardiovascular renal disease, the diffuse nature of the pain, radiating to the back, the maintenance of good heart tones and high systolic blood pressure, the absence of evidence of congestive failure and of clear cut evidence of intra-abdominal pathology, a diagnosis of dissecting aneurysm of the aorta was made by the staff physician (M. F. G.).

Laboratory examination showed 2 plus albumin and 4 plus acetone and diacetic acid in the urine. The blood examination revealed 14.3 gm. (103.3 per cent) of hemoglobin (Osgood-Haskins), 4.09 million red cells, 9,900 white cells, with a normal differential count. The sedimentation rate by the modified Westergren method [6] was 12 mm. in 15 minutes and 20 mm. in 45 minutes, increasing to 45 mm. in 15 minutes and 97 mm. in 45 minutes by the fifth day. The blood urea nitrogen was 14.50 mg. per 100 c.c. of blood. The icterus index was 7. The Kolmer and Kahn were negative at this time.

A roentgenogram (figure 1) of the chest showed deviation of the upper mediastinum to the right and an enlarged heart of aortic configuration with evidence of an aneurysm of the descending limb of the aorta.

The electrocardiogram (figure 2) showed left axis deviation, regular sinus rhythm, an inverted T-wave in Leads I and II, and a depressed S–T interval in Lead I.

For the first few days the patient had a slight fever. The pain remained about the same in character but was relieved by morphine sulphate, 10 mg. every four hours; a little later paraldehyde, 8 c.c., once or twice in 24 hours, controlled the pain. The pain and temperature gradually decreased and the patient was discharged Dec. 16, 1934, 59 days after entrance.

He reëntered the hospital Feb. 16, 1935, complaining of shortness of breath, swelling of the ankles, chest pain, headache, dizziness, spots before the eyes, palpitation of the heart, and weakness. Since his discharge the previous December, the pain, though much diminished, had persisted, and there was some shortness of breath and swelling of the ankles associated with nocturia of three to four times. This condition persisted until Feb. 16, 1935 when he was again incapacitated by the increase in lower chest pain and shortness of breath. The dyspnea was so severe that he was forced to sit up in bed. The pain at times radiated through to the back and down the inside of the right arm.

Physical examination showed extreme orthopnea, flushed face, nervousness, and marked pulsation of the carotid vessels. The blood pressure was 135 systolic and 110 diastolic; the respirations were 30; the pulse, 100 and regular; the temperature, 99° F. (37.3° C.). The chest showed bilateral basal moisture. The cardiac findings were the same as at the previous examination. The trachea was slightly deviated to the

right. There was some engorgement of the systemic veins. The liver was tender but not enlarged. There was no edema of the ankles.

The laboratory examination was essentially the same as on the previous entrance.

An electrocardiogram (figure 3), Feb. 18, 1935, showed a regular sinus rhythm, a left axis deviation, a depression of the S–T interval in Leads I and II and a high

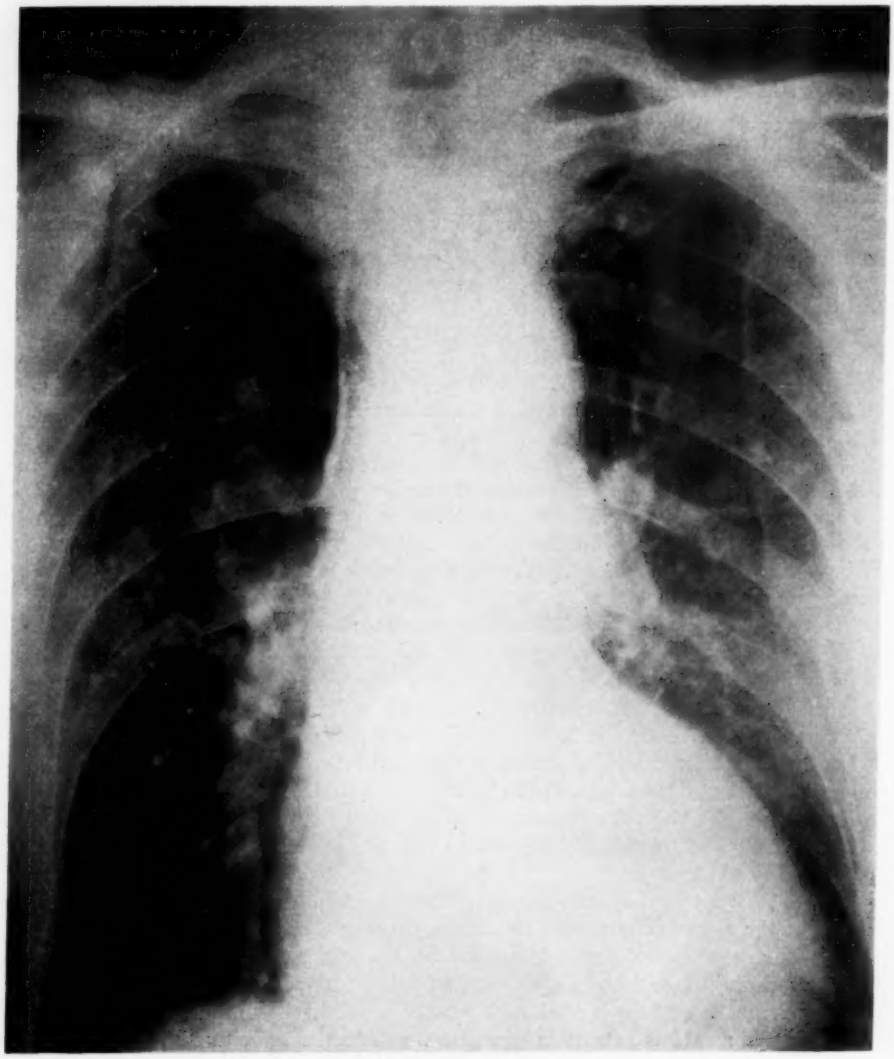

FIG. 1. Roentgenogram of the heart in Case 1, taken Oct. 18, 1934. Note the aneurysmal dilatation of the descending aortic arch, the aortic configuration of the heart and the deviation of the trachea to the right.

take-off in Lead III, and a diphasic T-wave in Lead I. These findings were strongly suggestive of a recent coronary thrombosis and differed decidedly from the previous tracing.

The patient expired suddenly five days after admission.

Necropsy revealed pericardial tamponade due to hemorrhage from intrapericardial perforation of a recent dissecting aneurysm confined to the ascending aorta. In addition, an old dissecting aneurysm extending from the arch of the aorta into the common iliac arteries was found. The walls of this aneurysm were completely reendothelialized. The heart weighed 650 gm. Serial sections of the coronary arteries

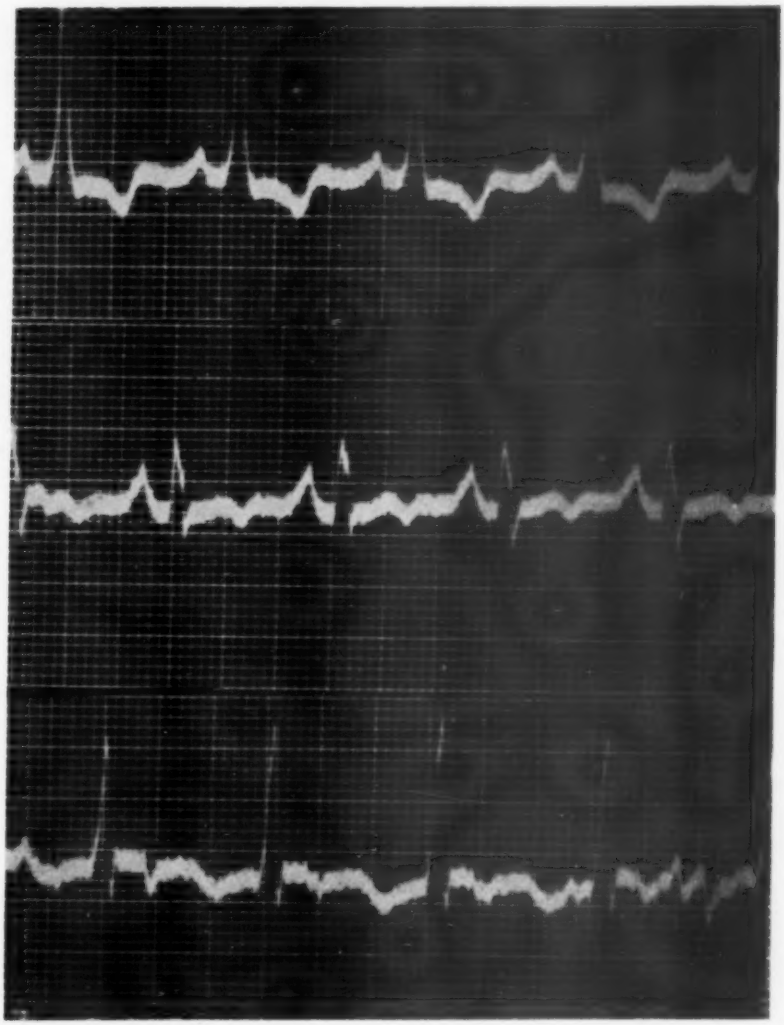

FIG. 2. Electrocardiogram in Case 1, taken Oct. 26, 1934. Note the negative T-waves in Leads I and II and the evidence of left axis deviation.

showed numerous atherosclerotic plaques but the lumens were widely patent. The myocardium showed no fibrosis. The final anatomic diagnosis was perforation of dissecting aortic aneurysm with hemorrhage into the pericardial sac; dissecting aneurysm of the aorta and common iliac arteries, and syphilitic aortitis.

Case 2. R. A. Y., a huge white man, aged 43, entered Multnomah County Hospital at 3:30 p.m., Jan. 28, 1935, complaining of severe tearing pain in the chest, ab-

domen, and back. He had felt well until Dec. 25, 1934, when, following a heavy Christmas dinner, he called a physician for an attack of "indigestion." The physician told him he had high blood pressure and that he had had a heart attack. A second similar attack occurred Jan. 5, 1935, following which he returned to his work as a boiler fireman. He was awakened at 11:00 p.m. Jan. 27, 1935 by a mild pain in the chest which at 1:00 a.m. became suddenly very severe and tearing in character as if

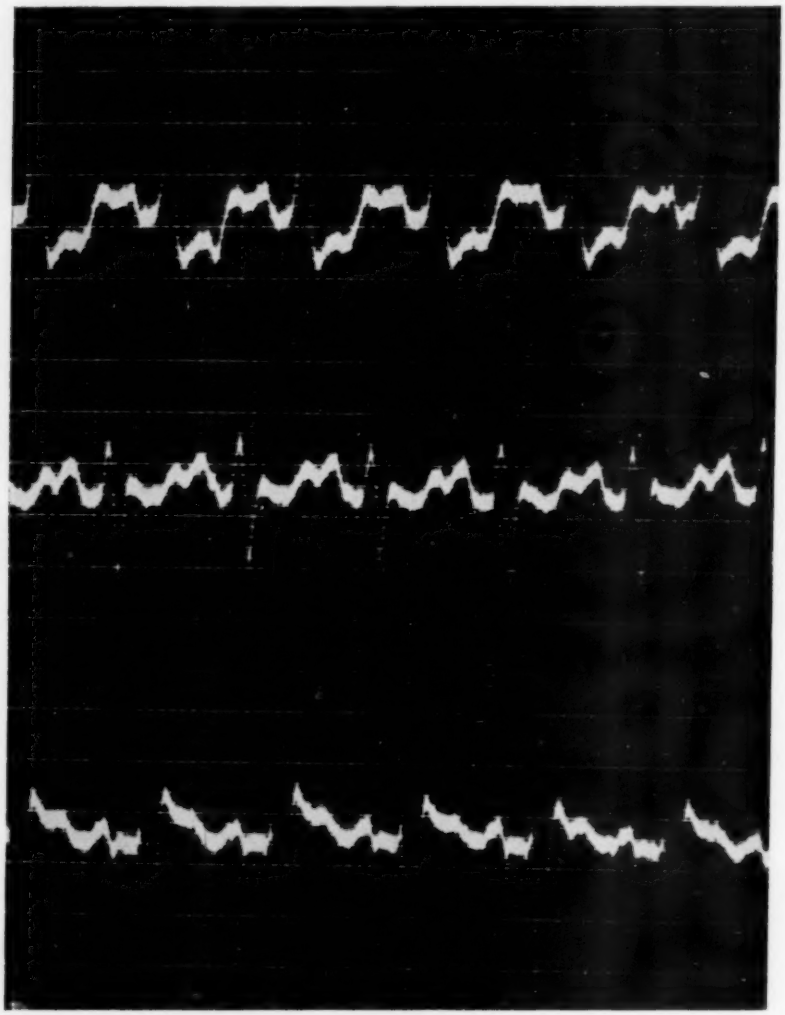

FIG. 3. Electrocardiogram of Case 1, taken Feb. 18, 1935. Note the marked change from the previous electrocardiogram and the evidences of coronary occlusion, although none was found at necropsy.

"something had broken" in his chest. The site of maximum intensity of the pain changed from the front of the chest to the left shoulder and then to the abdomen and the lumbar region. The pain became excruciating and he vomited once at 4:00 a.m. The pain had continued unabated, notwithstanding two hypodermic injections, presumably of morphine.

Physical examination revealed a powerfully built man weighing 297 pounds, obviously in severe pain. The temperature was 99.2° F. (37.3° C.); the pulse, 93; and respirations, 20 per minute. The blood pressure was 260 systolic and 145 diastolic. The fundi showed notching of the veins and narrowing of the arteries. A vigorous carotid pulsation was noted on the right side of the neck. The heart was markedly enlarged, of aortic configuration with a forceful apex beat, regular rhythm,

FIG. 4. Electrocardiogram of Case 2, taken Feb. 4, 1935. Note the diphasic T-waves in Leads I and II, the depressed S–T interval in Lead I and the elevated S–T interval in Lead III as well as the left axis deviation.

a loud booming aortic second sound, but no murmurs. The peripheral vessels showed 2 plus thickening of the "rubber tube" type characteristic of hypertensive cardiovascular renal disease.

Laboratory studies revealed a 2 plus albuminuria with hyaline casts, normal red cell count and hemoglobin, an icterus index of 18, a white cell count of 10,000 with 67

per cent segmented neutrophiles and 3 per cent staff cells. The sedimentation rate was 55 mm. in 15 minutes and 85 mm. in 45 minutes. The blood urea nitrogen was 17 mg. per 100 c.c. of blood. The Kolmer and Kahn tests were negative.

The electrocardiogram (figure 4) showed a regular sinus rhythm with a rate of 88, a P–R interval of 0.18 second, a diphasic T_1, a depressed S–T interval in Lead I, a high S–T interval in Lead III, and left axis deviation.

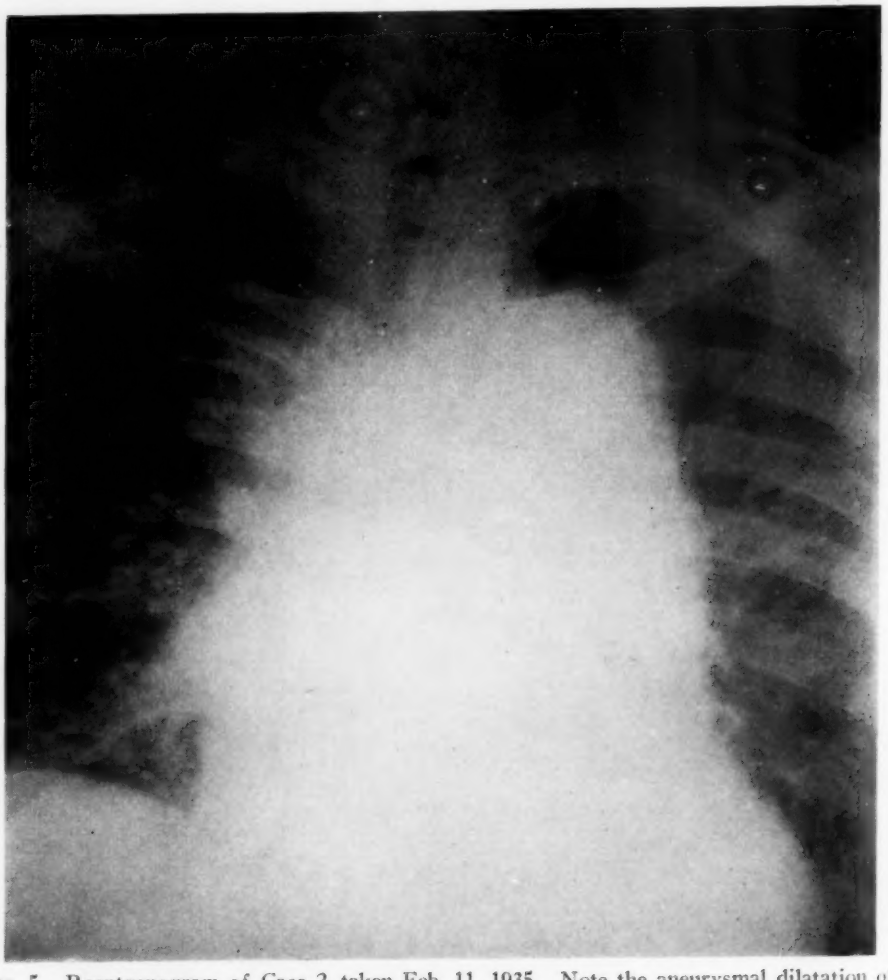

FIG. 5. Roentgenogram of Case 2, taken Feb. 11, 1935. Note the aneurysmal dilatation of the aorta and the deviation of the trachea to the right.

A six foot roentgenogram (figure 5) of the chest revealed passive congestion at the bases of both lungs, a greatly enlarged heart of aortic configuration with a widened, distorted aorta shadow of increased density displacing the trachea to the right but showing no saccular dilatation.

The pain in the chest and back persisted until his death, February 17. It was not affected by a test dose of nitroglycerine and was only partially relieved by 15 to 30 mg. of morphine sulphate administered every three to four hours until death. February 12, a systolic murmur was noted over the dorsal and lumbar spines with

the point of maximum intensity at the level of the tenth dorsal spine. The blood pressure maintained a level of about 240 systolic and 140 diastolic. The pulse rate varied between 80 and 100 and the temperature between 97.0° F. (36.1° C.) and 100.0° F. (37.8° C.). At 2:30 a.m., February 17, the patient was sleeping when seen by the nurse. At 3:30 a.m., he was found dead in bed.

A clinical diagnosis of hypertensive cardiovascular renal disease with acute coronary thrombosis was made on admission by the intern (R. L. B.). The tearing quality of the pain and its radiation to the back with no signs of congestive failure and no fall in blood pressure suggested the diagnosis of dissecting aneurysm of the aorta to the staff physician (E. E. O.). This diagnosis was confirmed by discovery of the murmur radiating down the spine, by the findings in the roentgenogram, and by the icterus index. The final clinical diagnosis was dissecting aneurysm of the thoracic and abdominal aorta with terminal rupture, hypertensive cardiovascular renal disease with left ventricular hypertrophy, regular sinus rhythm, and familial obesity.

Necropsy revealed hypertrophy and dilatation of the left ventricle and a dissecting aneurysm extending from the level of the attachment of the ductus arteriosus to the bifurcation of the aorta, with a perforation just beyond the arch into the left pleural cavity into which a massive hemorrhage had occurred. Microscopically, sections of the aorta revealed many small scars in the media with lymphocytic infiltration about the vasa vasorum. An organized blood clot was attached to one side of the split media. The intima was thickened and diffusely infiltrated with lymphocytes and plasma cells.

Discussion

Dissecting aneurysm, or aneurysm dissecans, of the aorta is characterized, clinically, by the sudden onset in a patient with hypertension, of severe, tearing pain in the chest, usually radiating to the back, followed, after a variable interval, by sudden death; and is characterized, pathologically, by a primary rupture of the intima with a splitting of the media, and a secondary rupture externally or, less commonly, back into the lumen.

Etiology. The exciting cause in nearly all cases is hypertension. The cause of the hypertension is usually hypertensive cardiovascular renal disease, less commonly nephritis. Thirteen cases have been reported in patients with coarctation of the aorta and one [7] in a patient with basophile adenoma of the pituitary. The usual predisposing cause is a sudden rise in blood pressure due to excitement, exertion, trauma, distention of the stomach, or vomiting. A history of static strain as in wrestling, lifting, or straining at stool is especially common. The age distribution is that of the diseases causing the hypertension. The youngest cases are those with coarctation of the aorta or nephritis. The majority occur between the ages of 40 and 70 when hypertensive cardiovascular renal disease has its greatest incidence. The condition is more common in males (65 per cent) than in females probably because of the greater exposure to unusual strain.

The rôle of syphilitic aortitis is controversial. Loeschke,[8] 1928, believed that syphilis had a tendency to bind the aortic wall, thus preventing wide dissections. Kellogg and Heald,[3b] 1933, stated: "It seems probable that the lesions of syphilis in the aorta, being more focal in their intensity, lead to a localized rather than a generalized weakening of the wall. . . ."

Samson,[3a] 1931, said: "It seems probable that a luetic meso-aortitis, through an interference with the blood supply leads to a degeneration of the medial fibers, and a somewhat displaced arrangement, saccular aneurysm being the sequel instead of the dissecting type." Shennan,[1] 1934, feels that syphilis may play a dual rôle in the production of dissecting aneurysm. In some cases it seems that the process is not sufficiently established to resist the splitting of the laminae; and in others, a toxic necrosis of the muscularis, in the absence of infiltration and adventitial changes, so weakens the aortic wall as to allow wide dissection. The association of the two conditions seems to us to be merely a coincidence. We do not believe syphilitic aortitis either predisposes to, or prevents, dissecting aneurysm. The incidence of syphilis (10 per cent) in patients with dissecting aneurysm is not materially greater than the incidence of syphilis in the general population of this age and sex group. The site of rupture is usually in an area of medial degeneration of the type occurring in hypertensive cardiovascular renal disease rather than at the site of a syphilitic lesion. Syphilis is certainly not an important predisposing factor because the great majority of the patients had no clinical or pathologic evidence of this disease, and in the cases which were associated with syphilitic aortitis there was usually coexistent hypertension or otherwise unexplained left ventricular hypertrophy.

Pathology. The pathology has recently been thoroughly discussed by Shennan [1] and most of the statements that follow are summarized from his data. Dissecting aneurysm is noted once in every 300 to 500 necropsies.[3c] The essential pathology is a rupture of the intima with a splitting of the media. In most instances there is a secondary rupture externally and, in a few cases, secondary rupture back into the lumen of the aorta.

In about 70 per cent of the cases the initial rupture is in the ascending aorta, in about 20 per cent in the transverse arch, and in about 10 per cent in the descending thoracic or abdominal aorta. The length of the dissection varies from a few centimeters to the entire length of the aorta and occasionally extends as far down as the popliteal arteries. In about 30 per cent of the cases the dissection is confined to the ascending or transverse arch, and in about 35 per cent the abdominal aorta is involved. Usually the major dissection is in a distal direction, but in about 10 per cent of cases it is in a proximal direction.

In about 95 per cent of cases, death is due to secondary rupture of the aorta. Seventy per cent of cases rupture into the pericardial sac, 20 per cent into the left pleural cavity, 5 per cent into the mediastinum, and a few cases into the right pleural cavity, the abdominal cavity or the retroperitoneal tissues. One reported case ruptured into the pulmonary artery.

The most constant associated pathology is left ventricular hypertrophy, present in about 85 per cent of the cases reported. Some degree of medial degeneration is usually demonstrable. Syphilitic aortitis is associated in about 10 per cent of all cases. Atheromatous changes are present in about

50 per cent of the cases, as might be expected from the age distribution, but the atheromatous lesions show little relation to the dissection.

Shennan [1] discusses the various theories of pathogenesis and concludes that medial degeneration is the most important factor. From the analysis of his data and the other reported cases, it seems to the authors that hypertension is by far the most important factor in the pathogenesis.

Clinical Characteristics. The patient is usually first seen just after the sudden onset of severe pain in the chest and back. Questioning may elicit a familial history of a "stroke" or high blood pressure; and a past history of high blood pressure, nocturnal polyuria, or occipital headaches suggestive of hypertensive cardiovascular renal disease. In younger patients there may be a history characteristic of preëxisting nephritis or coarctation of the aorta. The pain usually begins following excitement, exertion, or injury. It is described as sharp, tearing, or as if something had broken in the chest. Its point of maximum intensity is usually over the middle or upper sternum and its most common radiation is into the region of the mid-dorsal spine. It may radiate to the abdomen, lumbar region, shoulder blades, neck, or down the arm. Its segmental distribution is likely to be higher than that of coronary artery disease.[10] It is often diffuse, localized with difficulty, and is usually very severe, requiring large doses of morphine to control it. It is associated with extreme restlessness and persists unabated for many days. There is a tendency to sudden exacerbations in intensity with migration of the points of reference, indicating the development of further dissections. Dysphagia is sometimes present.

Physical examination reveals an apprehensive individual, obviously in severe pain. Cyanosis and dyspnea are often present. Fever of slight degree is common. The increased rate of pulse and respiration is probably secondary to the severe pain. The blood vessels show the "rubber tube" type of thickening, characteristic of hypertensive cardiovascular renal disease. Unless in shock, the blood pressure is high. It may be lower in the left arm or in the lower extremities than in the right arm. Absence of the pulse in the left arm, carotids, or inferior extremities has been recorded. The trachea may be deviated to the right. Percussion of the heart reveals an aortic configuration with dullness under the upper sternum. Signs of congestive failure are usually absent. The aortic second sound is typically accentuated but murmurs over the heart are not characteristic. Auscultation over the dorsal and lumbar spines, the abdominal aorta, or the femoral arteries may reveal a systolic murmur transmitted downward. This may develop late in the course of the disease, so should be looked for daily. Coarctation of the aorta may produce a similar murmur but may be recognized by finding its characteristic collateral circulation. Signs of obstruction of any branch of the aorta may be present. Among these signs are coma, hemiplegia, anuria, gangrene of the extremities, paralytic ileus, or localized swellings over the chest, neck, or abdomen.

Sudden death supervenes within a few minutes in 65 per cent of the cases, a few days in 10 per cent of the cases, and after an interval of weeks to months in the majority of the remainder, although a few cases have been known to live for years. Death is due to rupture of the aorta, usually into the pericardium, less commonly into the pleural cavity, mediastinum, or abdomen. While only of academic interest, the site of rupture may be determinable after death by percussion of the absolute cardiac dullness, the lung fields, and the abdomen.

The most valuable laboratory change, when present, is an increase in the icterus index due to bilirubin formation from hemoglobin destruction in the clotted blood. Urobilinogen may be increased in the urine but bile pigment does not appear. Clinical jaundice is usually absent but occasionally slow hemorrhage may occur into the mediastinum or retroperitoneal tissues of sufficient extent to produce it as well as an anemia. A moderate neutrophilic leukocytosis is often present. Serologic tests for syphilis are usually negative but a positive test does not exclude this diagnosis. Renal function may be decreased or normal as in any patient with hypertension and should be determined.

Roentgenographic features have been well summarized by Wood, Pendergrass and Ostrum.[9] These features consist of a diffuse widening along the shadow of the aortic arch with diminished pulsation, an enlarged heart of aortic configuration, displacement of the esophagus and trachea to the right, shadows of dissections along the branches of the aorta and evidences of fluid in the left pleural cavity.

The electrocardiogram shows nothing characteristic of this condition but frequently shows left axis deviation and evidences of myocardial damage from coronary disease as is common in any case of severe hypertension. If clear cut evidence of recent coronary thrombosis is absent the electrocardiogram is helpful, but evidence of coronary occlusion does not exclude dissecting aneurysm. The changes usually ascribed to coronary occlusion may occur in dissecting aneurysm when necropsy fails to reveal evidence of infarction as was true in our two cases.

Diagnosis. The diagnosis of dissecting aneurysm should not be difficult if this possibility is given adequate consideration. This diagnosis should be considered in any patient who develops sudden pain in the chest or who dies suddenly. Evidences of co-existing hypertensive disease, radiation of the pain to the back, migration of the pain, and the increase in the icterus index are the most helpful features. Evidences of congestive failure are usually absent. If, in addition, a systolic murmur over the dorsal and lumbar spines develops and coarctation of the aorta is excluded, the diagnosis becomes almost certain. The sequence of sudden chest pain followed by sudden death is in itself strongly suggestive of this condition.

Dissecting aneurysm must be differentiated from coronary occlusion, from syphilitic aneurysm, from pulmonary embolism, and from the other

causes of sudden death. The great majority of the reported cases of recent years were erroneously diagnosed as cases of coronary occlusion.

The differential diagnosis of coronary occlusion is not complete without a consideration of dissecting aneurysm. The chief points of differentiation are the radiation of pain to the back, the migration of pain, and the elevation of the icterus index in dissecting aneurysm; and in coronary occlusion the occurrence of pericarditis, and signs of myocardial degeneration such as a fall in blood pressure, congestive failure and typical electrocardiographic changes. Radiation of pain to the back is extremely rare in coronary occlusion and radiation to the lumbar or sacral regions is almost unknown. Pain in coronary occlusion is usually described as constricting or vise-like, that of dissecting aneurysm as tearing or as if something had broken. The elevation of the icterus index has not heretofore been described, but it is logical to expect that it would be present in most cases of dissecting aneurysm if studied between 12 hours and two weeks after the time of onset. The two conditions not infrequently coexist so that, contrary to some authors,[3c] electrocardiographic evidence of coronary occlusion does not exclude dissecting aneurysm. Sudden death from rupture of the heart may follow a coronary occlusion.[11] These cases may be especially difficult to distinguish from cases of dissecting aneurysm with rupture into the pericardial sac.

Syphilitic aneurysm of the aorta is not necessarily associated with hypertension and rarely causes pain for the first time with the dramatic suddenness characteristic of dissecting aneurysm. It is usually preceded by a history of substernal oppression and syphilis, and is often associated with aortic regurgitation, or a ringing aortic second sound, or with laboratory or clinical evidence of syphilis. The greatest difficulty in differentiating syphilitic aneurysm from dissecting aneurysm will be encountered in those cases first seen after sudden death from rupture as both types of aneurysm may rupture into the same locations.

Pulmonary embolism may produce death with equally dramatic suddenness but occurs usually in patients who have been in bed for some length of time or who have chronic right sided cardiac dilatation.

Cases of traumatic dissecting aneurysm seen in shock might be confused with internal hemorrhage from a ruptured viscus but the arterial and cardiac evidences of preceding hypertension should be of help and the subsequent course decisive. All aneurysms secondary to trauma are of the dissecting type.

Coarctation of the aorta must be excluded in cases with a systolic murmur transmitted down the spine because it is the only condition other than dissecting aneurysm giving rise to this type of murmur. The collateral circulation in the back and roentgen evidence of erosions of the lower margins of the ribs characteristic of coarctation should be most helpful because both conditions may result in a lower blood pressure in the inferior extremities

than in the upper. Coarctation of the aorta and dissecting aneurysm may coexist.

Prognosis. The prognosis is very grave. Sixty-five per cent of the cases so far reported have died from perforation within a few minutes and 10 to 15 per cent more have died within a few days of the onset. Most of the remainder died within a few weeks or months but cases have been reported that have lived for many years. Most of these proved to be cases that have reperforated into the lumen of the aorta.

Treatment. The most important point in the treatment is absolute rest with avoidance of all types of strain which tend to raise the blood pressure. Education in methods of avoiding such strains in persons with an extremely high diastolic pressure may prevent the development of this condition. As soon as the condition is recognized, large doses of morphine should be given to allay the extreme pain and anxiety and should be repeated as necessary until the pain can be controlled by other medication, usually a matter of weeks. Special nursing care to relieve the patient of the necessity of making any exertion on his own behalf is desirable during the first week. Mineral oil and mild laxatives should be given to secure a soft enough bowel movement so that there is no necessity for straining. Bleeding and administration of nitrites would seem logical procedures if the blood pressure is markedly elevated. Just how long the period of rest should be continued is difficult to say but it certainly should be a matter of months after all pain has ceased, and the return to physical activity should be very gradual. The diet should be soft and adapted to the needs of the patient as regards calories and quality, taking into consideration the body weight and build, and the renal function. Symptomatic therapy should be given as indications arise.

Summary and Conclusions

Dissecting aneurysm should be diagnosed during life but only a few cases have been clinically recognized. Two cases diagnosed during life are reported. The essential features of the condition are summarized and the criteria which may aid in the recognition of this condition are given. If dissecting aneurysm of the aorta is considered whenever severe pain radiating to the back develops suddenly in a patient with hypertension and the case is analyzed by the methods here outlined, a correct diagnosis should usually be made. Careful analysis of the history is the most important single feature.

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DIET OF THE BLUFF DWELLERS OF THE OZARK MOUNTAINS AND ITS SKELETAL EFFECTS *

By E. G. WAKEFIELD, M.D., *Rochester, Minnesota,* and SAMUEL C. DELLINGER, *Fayetteville, Arkansas*

IN another study we presented data on the diseases of bone which were prevalent among an ancient primitive race of people who inhabited the shelters of the bluffs in the Ozark Mountains of Arkansas and Missouri. The period of their occupation, from whence they came, or where they went are questions which cannot be answered. The absence of smooth stone or iron gadgets among their burial effects is mute evidence that they lived in ancient times and that they were very primitive people. Whether they lived twenty, thirty, or more centuries ago is irrelevant in this study.

In making a study of the osseous remains, the age of the bones is not as important as is the state of preservation. In the museum of the University of Arkansas there are four or five skeletons of children which are in a good state of preservation, and the isolated parts of many more. We believed that this number of bones of children of an extinct race, combined with a study of a great number of adult bones, would serve to indicate whether there was, at least, a tendency toward the development of deficiency diseases. In this material there also were several parts of bodies which were mummified. We were particularly interested in these mummified parts, in the hope that we could find some feces which we could examine for the presence of ova or parasites.

For burial, the bodies were usually flexed and placed in crude feather-down bags or under pieces of baskets. In or near the body were deposited various objects which were mute evidence of the meagerness of the food and clothes which these people possessed. They apparently cultivated corn, sunflowers, gourds, pumpkins, squash, pigweed, lambs-quarters, and beans, presumably for food, as many of these seeds were found in the caches. They had means of procuring fish, mammals and birds, as many bones of these animals were found in the caches and in the bluffs which these people inhabited. Thus, the data obtained from the caches indicate that these people lived on a mixed diet, if they ate what we assume they did. In the case of one of these people, we do not have to assume what was eaten during the last days of life. In an exceptionally dry shelter, where characteristic caches were found, there was a part of a dried body. The tissues of the lower part of the abdomen, pelvis, left leg to the middle third of the thigh, and the right leg and foot were dried and shrunken but well enough preserved so that the distal third of the large blood vessels of the abdomen, the sigmoid flexure of the colon, and the rectum could be definitely identified.

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From the Division of Medicine, The Mayo Clinic, and the Department of Zoölogy, University of Arkansas.

In the rectosigmoid or rectum were dried pellets of feces (figure 1), which were removed by means of long tissue forceps. The situation of this material obviates any question as to its true nature. The only questionable feature is whether this person might not have been buried more recently than has been assumed.

The present natives of this district do not bury their dead in these shelters. The American Indian in this part of the country did not utilize these shelters for any known purposes. There were no "top layer cultures" in any shelters of this immediate district. A fugitive from justice might be considered as a possibility. This possibility is ruled out because the remains from which the feces were obtained were those of an elderly woman.

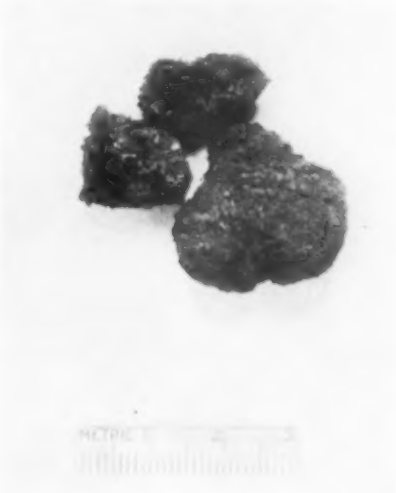

FIG. 1. Pellets of feces obtained from mummified body.

The identification of the remnants of food particles in the feces was most interesting. This work was done at the Bureau of Biological Survey, United States Department of Agriculture, by Clarence Cottam and his staff, who are in charge of Food Habits and Wild Life Research. They were aided by various members of other divisions and bureaus. The report was as follows: "Our office has examined the material and we find that the principal food item consisted of the fruit of the sumac (Rhus? Capallina). The other common food item consisted of ground acorns (Quercus), apparently black oak (Quercus velutina). Incidentally this is a common species of oak occurring in Arkansas. In addition to these two items, there seems to be a little unidentifiable vegetable material, perhaps from some fruit substance. There was also a fair amount of charcoal which may have been eaten deliberately or mixed with the food. At any rate it was well mixed with the material submitted.

" Within the intestinal material were two small early stage coleopterous larvae of the family Nitidulidae. Dr. A. G. Boving of the Bureau of Entomology and Plant Quarantine believes that these probably belong to the genus Steliodite. Most species of this family of small beetles feed on the juices of fruits, fermenting sap, dried or stored fruits, and a few feed on flowers, fungi and carrion.

" The photograph (figure 2) accompanying your letter is stated by Dr. H. W. Ewing of the Bureau of Entomology and Plant Quarantine to represent some species of mite of the family Tyroglyphidae. Members of this family feed largely on stored food products and decaying materials.

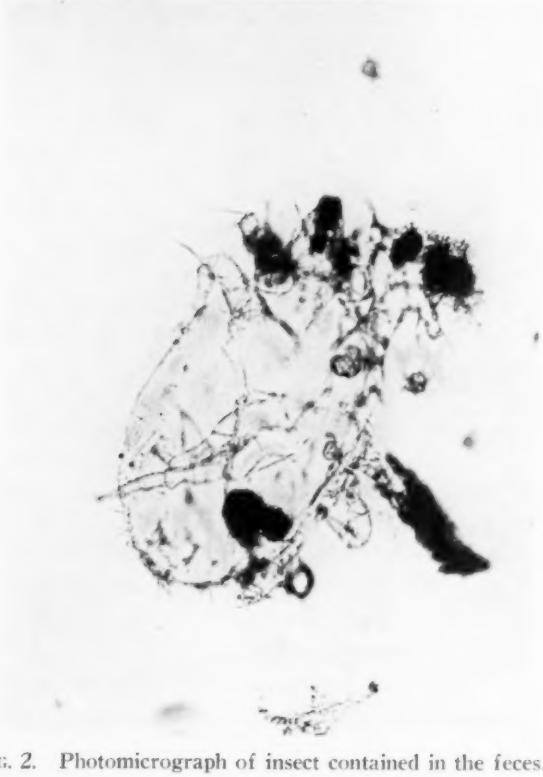

FIG. 2. Photomicrograph of insect contained in the feces.

" In addition to these, a fragment of an ant (Formicidae) and a number of lice and mites have been transmitted to specialists for further study. I will communicate with you further as soon as we obtain more specific identification of the minute items held out.

" A fungus growth was found on some of the material which undoubtedly developed after the individual was buried. It seems entirely possible that the insect material may have been taken accidentally or incidentally with the food and probably as a result of not being unduly selective in the choice, nor insisting on a high degree of sanitation. It seems probable that this represents a winter food."

The report on the foregoing material was as follows: "Coleopterous larva belonging either to the family Nitidulidae or one of the small families relating to the Nitidulidae, possibly the Monotomidae. Definite determination cannot be given from the two fragments. Det. A. G. Boving.

"A few specimens of a species of *Cheyletus,* a predacious mite that feeds largely on other mites.

"Fragments of a species of the family Tyroglyphidae. Det. H. E. Ewing."

We were very anxious to find intestinal ova or parasites, if any were present. Many searches of the material have been made by Dr. T. B. Magath, but all these failed to reveal ova or parasites. A pellet of the feces was cracked and cultures were made from the center, but neither spore-forming nor non-spore-forming microörganisms grew. Tests for bile were negative. Quantitative chemical analyses of the feces were done by Dr. Mildred Adams; the results of these analyses are shown in table 1.

CHEMICAL ANALYSES OF FECES OF AN OZARK BLUFF DWELLER AND FECES OF A NORMAL PERSON

	Normal Feces Percentage of Dried Weight	Feces of an Ozark Dweller Percentage of Dried Weight
Nitrogen	5.10	4.77
Calcium	3.10	4.37
Magnesium	0.67	0.50
Sodium	1.00	0.67
Potassium	2.00	3.92
Phosphorus	1.70	1.63

Several of the crude cradles obtained from these shelters during the excavations were smeared with material which probably was feces. In this material there was an occasional insect, but nothing which resembled food material, intestinal ova, or parasites.

We have objective data which indicate that these people ate the fruit of the sumac, and acorns. We have circumstantial evidence that they ate corn, pumpkins, squash, sunflowers, lambs-quarters and beans, and the flesh of mammals, fish and birds. One can imagine that the food supply of these people was uncertain. However, they stored many of the natural foods which were gathered from the forests, such as hickory nuts, chincapins and acorns, and their cultivated crops of corn, sunflowers and other seeds for winter consumption and spring planting. These crops must at times have been limited and uncertain. These people did not possess sufficient implements to carry on more than a limited amount of agriculture, nor did they possess sufficient weapons to obtain a very great amount of meat by hunting. Their hunting equipment consisted of spears, darts, crude axes, and, of course, sticks and stones. It is of sufficient importance here to mention the fact that almost invariably they split the bones of the animals utilized for meat, in order to obtain the marrow for food. This splitting of the bones was probably done on account of the scarcity of meat.

The teeth of both the children and the adults were generally very good (figure 3). There was no evidence of either congenital or acquired diseases.

At the present time, it is recognized that ossification occurs earlier among females than it does among males. In the newly born this difference of ossification may be one of days, while later in life the time at which fusion of the epiphysis occurs may differ by years in the two sexes. There is some evidence to suggest that ossification occurs earlier among children who are well cared for than it does among children who are neglected and underfed.

Many factors appear to influence ossification, which is the determining influence on normal shape and size of the adult bone. Some of these factors are fresh air, food, sunlight (or ultraviolet light) and exercise. Ossification is advanced in certain conditions, such as pubertas praecox, and

FIG. 3. Teeth of an adult of this race.

is retarded in disorders of certain endocrine glands, such as dysfunction of the thyroid gland or pituitary body.

It is evident that the bluff dwellers possessed all the necessary requisites for the production of normal skeletal systems. Food may have been abundant enough at times, but the supply was uncertain. The food supply of the growing children after the period of nursing undoubtedly was uncertain, and according to present standards, it was meager; however, normal skeletons did develop. The possible influences of dysfunction of the thyroid gland or pituitary body have been carefully considered. There were no examples of disturbances in growth and development which would suggest dysfunction of these glands.

The femurs and tibias of a child were put aside for study on account of their lightness of weight and increased transverse diameters at the distal ends. So light and fragile were these bones that great care had to be ex-

ercised in handling them, and in spite of this care the lower end of the right femur was broken. Satisfactory roentgenograms were difficult to obtain on account of the thinness of these bones. At the distal ends of these femurs and at both ends of the tibias there were dense transverse lines in the roentgenograms; otherwise the roentgenologic appearance of these bones was normal. These lines serve to indicate periods of growth. In the absence of any more marked deformities than were present in the lower ends of

FIG. 4. Maximal amount of anterior bowing of tibias of this race.

these femurs or in their condyles, and because of the minimal degree of anterior bowing of the tibias, a definite diagnosis could not be made. However, these bones were not normal, and without doubt this child had suffered a prolonged illness with secondary dietary deficiencies.

There were two adult tibias which showed anterior bowing and which were suggestive of rickets (figure 4).

The infant and adult skeletal remains of this primitive race of Americans impressed one by the absence of good evidence of rickets, scurvy and endocrine diseases or evidence of secondary deficiency diseases, which are common among present races. This absence of evidence of deficiency diseases is still more striking when one considers the possible effects of uncertain food supplies during that all important period of growth and development from five to ten years of age. The conclusion to be drawn is that this race possessed indomitable qualities in their germ plasm for the development of normal skeletons under adverse conditions and that this race also possessed a remarkable flexibility of digestive apparatus, which permitted them to eat large quantities of inferior, and perhaps unclean food and to utilize from it the so-called essentials of a normal diet. In other words, perhaps what is ingested in the way of food is not so important as how it is utilized in the process of alimentation and absorption.

The absence of findings indicating the presence of deficiency diseases in the Ozark bluff dweller is in keeping with studies made on other primitive races.[1]

Summary

The undigested food residue contained in the feces of an Ozark bluff dweller consisted of the fruit of the sumac, acorns, and insects. Their remains indicate that they had existed on a mixed diet of vegetable materials, meat and fish. No good evidence of primary dietary or endocrine deficiency diseases was found. This race must have possessed an indomitable germ plasm to be able to produce and maintain normal skeletal parts without evidence of deficiency diseases under most adverse dietary and sanitary conditions.

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CASE REPORTS

TERMINAL HEMORRHAGIC NEPHRITIS: A CASE EXEMPLIFYING THE PROTEAN CHARACTER OF ITS SIGNS AND SYMPTOMS*

By IRVINE H. PAGE, *New York, N. Y.*

CHRONIC hemorrhagic nephritis is a disease exhibiting signs and symptoms of protean character. So elusive are many of these that prognosis and effects of various treatments are often seriously misjudged. It is for this reason that the record of this patient, illustrating many of these pitfalls, is presented.

The Patient. This patient, a 49 year old woman, complained of swelling of the ankles beginning three years ago. The past history was irrelevant. Edema of the ankles began insidiously and was not associated with an obvious infection. Arterial pressure was found to be 200/120 mm. of Hg. Dr. Francis O'Connor, of Kingston, New York, who kindly referred her to us, has written that she complained at that time of severe headaches, spots before the eyes, and scanty urine. Red cells, casts, and protein were found in the urine. She was able to continue her work, but nine months later she seemed to be entering the terminal stage of nephritis. The blood pressure was 220/130 mm., non-protein nitrogen 44 mg. per cent, and creatinine 2.9 mg. per cent. Two months later she was admitted to this hospital.

She was a small woman appearing chronically ill and markedly anemic. Except for a slight amount of perivasculitis near the discs, the fundi were normal. All teeth had been removed. The heart was not overactive, nor was it enlarged. A_2 was accentuated and there was a soft systolic murmur heard over the apex. Arterial blood pressure was 196/110 mm. of Hg. Slight edema of the sacrum, ankles and legs (grade 2) was present.

The electrocardiogram showed the T-waves diphasic in Lead I, and negative in Leads II and III. R_2 was split and R_3 was both split and of low voltage. Atrioventricular conduction time was 0.22 second.

Renal efficiency, as measured by the urea clearance test of Möller, McIntosh and Van Slyke,[1] as recently described by Van Slyke, Page, Hiller, and Kirk,[2] was reduced to 13 per cent of normal. The maximum ability to concentrate glomerular filtrate as measured by the specific gravity of the urine was 1.009. Correction was made for the protein present in the urine, that is, 0.003 subtracted from the total specific gravity for each 1 per cent of protein. The number of formed elements in the urine was estimated by the technic of Addis.[3] On admission, 3,200,000 red blood cells were found in a 12-hour specimen of urine passed during the latter half of a 24 hour period, during which the patient received no fluids; 500,000 red blood cells are considered the upper limit of normal. Casts numbered 684,000, of which 80 per cent were granular and 20 per cent hyaline. Protein in the urine was estimated by the method of Shevky and Stafford.[4] The excretion amounted to 6 grams in 24 hours. Hemoglobin as recorded in terms of volumes per cent of oxygen capacity was reduced to

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From the Hospital of the Rockefeller Institute for Medical Research, New York, N. Y.

14.8, while 19.0 is the normal value for a woman of her age (see Peters and Van Slyke[5]). Gastric analysis showed free hydrochloric acid was not present even after histamine. Total acid was low, averaging only 7.0.

Gastric Analysis	Volume c.c.	Free HCl	Total Acid
Fasting	12	0	5.8
20 minutes after alcohol	17	0	7.4
40 minutes after alcohol	18	0	9.6
20 minutes after histamine	13	0	9.3

The Course

1. Edema, Plasma Proteins, Urinary Proteins and Diet. A diet of 2200 calories containing 80 grams of protein and 1.0 gram of salt was prescribed. Usually about one-half of the protein consisted of casein. Although the total plasma proteins were reduced to the level at which edema may appear, the albumin fraction was above the edema level. Fifteen days after admission the edema almost disappeared without a significant rise in either total plasma proteins or plasma albumin. This result was probably due to withdrawal of salt from the diet. Protein in the diet was raised to 100 grams. Urinary excretion of protein varied from 5 to 7 grams in 24 hours. After approximately one month, the dietary protein was reduced to 20 grams making up the deficiency of calories with carbohydrate. After 45 days of this régime no significant change in plasma proteins occurred, but urinary excretion fell slightly to 3 to 4 grams in 24 hours. Again the protein in the diet was raised to 100 grams and maintained at this level for five months. A slight rise occurred in the total plasma proteins, but no significant change was observed in the albumin fraction. Urinary protein excretion rose 5 to 6 grams, but fell toward the end of the period to an average of 2 to 3 grams. The protein in the diet was again reduced, this time to 30 grams, and maintained at this level for 4½ months, but no significant reduction of plasma or urinary proteins occurred. Two months after this period had started the patient had a severe hemorrhage from the descending colon which caused temporary slight depression of plasma protein. The following 11 months no restriction was put on her diet except that it contained the usual amounts of meat, and free salt was avoided.

This patient illustrates the fact that in patients who are well nourished and not losing large amounts of protein in the urine, protein in the diet may be varied within wide ranges without significantly affecting the plasma protein level or its excretion in the urine. But she remained free of edema only so long as salt was allowed in small amounts. It is of interest that although for 13 months the patient received not more than 1.5 gram of salt in her diet and excreted little more than a gram in 24 hours in the urine, she showed no signs of chloride deprivation. Examination of the serum after nine months on this low chloride intake showed that the chlorides were not significantly reduced, that is, 99.7 milli-equivalents per liter at pH 7.31.

2. Renal Efficiency. The urea clearance remained well below the level of 20 per cent of normal, which is the level set by Van Slyke and his associates[6] as that below which uremia may be expected to supervene. Except for insignificant variations, an average level of 10 per cent of normal was maintained for at least 19 months. Ability to concentrate urine was also reduced to a minimum.

3. Hemoglobin and Hematuria. Throughout the course in the hospital the hemoglobin fell slowly from 14.5 volumes per cent O_2 capacity to 11.2 shortly before death. A hemorrhage from the lower colon caused considerable loss at one time, but within two months it had regenerated to its original level. Reduced iron (3 grams a day) was fed during this period and may have aided in regeneration. Iron fed over a two-month period prior to this (the seventh and eighth months in the chart) had no significant influence on the level of hemoglobin. Hematuria was not pronounced until two months prior to death. Usually, however, the number of red cells excreted was

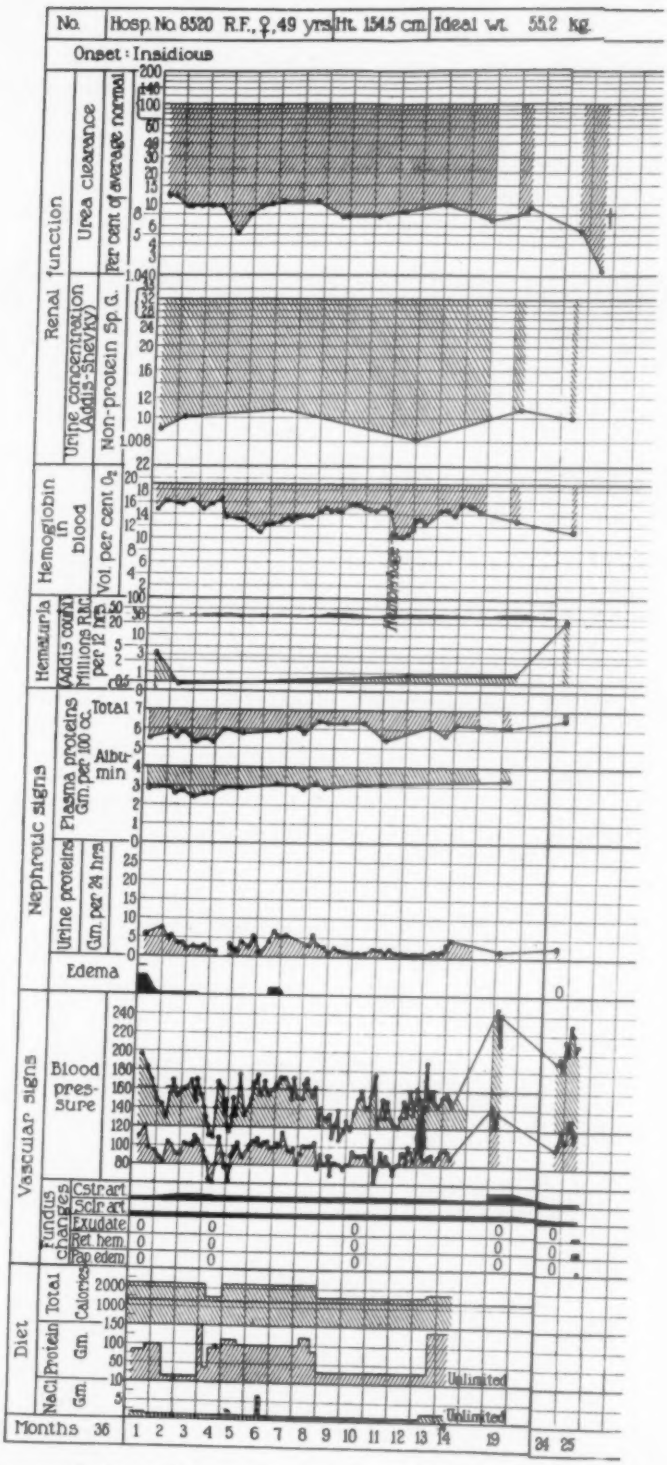

FIG. 1. Course of the patient as observed in the hospital. Blood pressure measurements were taken daily with patient in bed. They were averaged for convenience in charting. Fundus changes are represented as (*a*) arteriolar constriction, (*b*) sclerosis, (*c*) exudate, (*d*) hemorrhage, (*e*) papilledema. The first figure following the word "months" on the bottom line of the chart represents the probable date of onset.

slightly above normal. The loss of hemoglobin in the urine, at least as measured by the number of red blood cells, could not have contributed materially to the anemia.

4. Blood Pressure, Eyeground and Electrocardiographic Changes. Fluctuations in arterial blood pressure were great. For periods of weeks it was normal, only to rise again to an abnormal height. During the terminal six months it rose markedly and maintained the high level until just before death. Slight constriction of the retinal arterioles was usually observed. Sclerotic changes in them were also present, but of very moderate degree. It is of especial interest that not until a few days before death were hemorrhage, exudate, and papilledema noted.

The electrocardiograph changes were as follows:

On admission, T_1 diphasic, T_2 negative, T_3 negative, R_2 split, R_3 split and low voltage, conduction time 0.22 second.

Eighteen months later: T_1 negative, T_2 positive, T_3 positive, R_3 split and low voltage, conduction time 0.16 second.

Twenty-four months later: T_1 positive, T_2 diphasic, T_3 negative, R and $S_{1, 2, 3}$ low voltage, conduction time 0.18 second.

Although it was suggested on the basis of the prolonged conduction time that bundle branch block might develop, this did not occur. The size of the heart increased but moderately. Twenty days before death the measurements from a roentgen-ray plate were, maximum left 9.7 cm., maximum right 6.5 cm., and internal chest diameter 26.0 cm.

Terminal Stage. The terminal stage was of more than usual interest because of the long period of almost complete anuria during which she had but few symptoms. Four months prior to death she withstood an attack of bronchopneumonia in the North Country Community Hospital. Two months later vomiting began. It varied in intensity, but in general became progressively worse. Eighteen days before death the output of urine began to diminish and three days later had fallen to a low level (figure 2). As fluid intake was not reduced, her weight increased only to fall sharply five days before death.

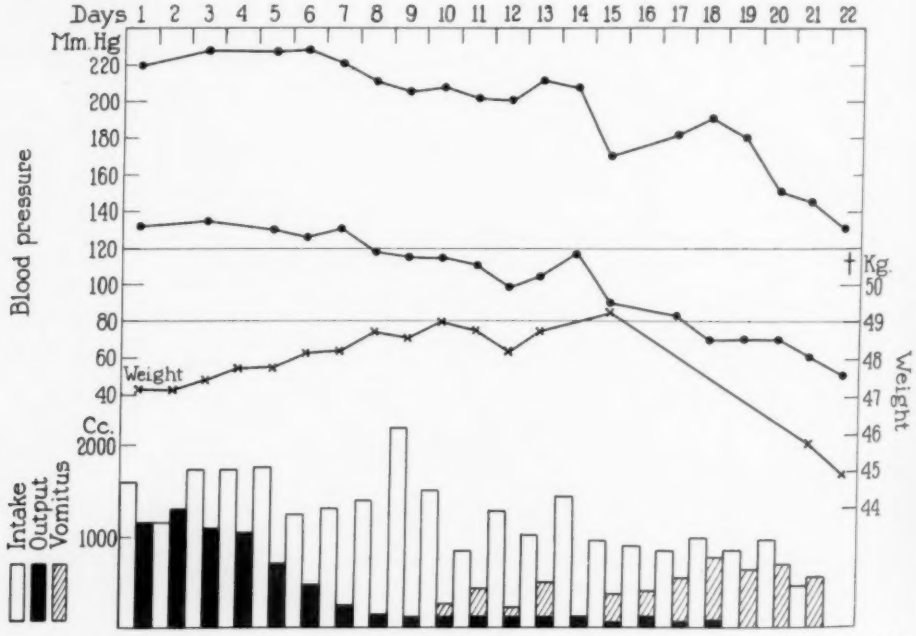

FIG. 2. Blood pressure, weight and fluid intake and output during terminal period in which almost complete anuria occurred.

Ten days before death urea clearance was 1.2 per cent of normal, and blood urea nitrogen 155.6 mg. per cent. Little change was noted in ability to concentrate urine, but marked hematuria had appeared. Hemoglobin was somewhat more reduced and plasma proteins a little increased. Blood pressure had risen from an average level of 156/98 to 242/140 mm. of Hg. Constriction of the arterioles of the fundi was more marked. About one month before death the eyegrounds were normal except

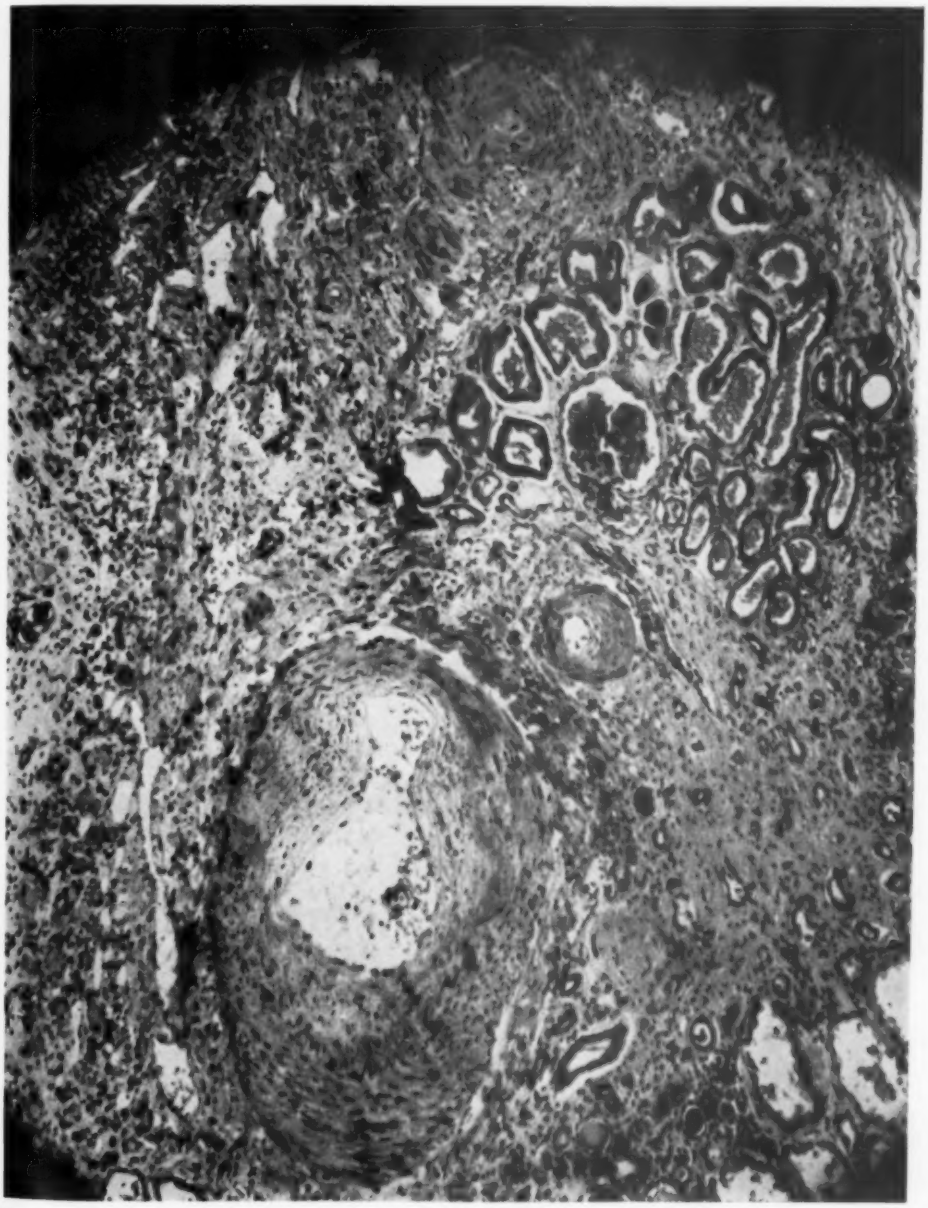

FIG. 3. Section of kidney showing marked thickening of the blood vessels, atrophied and dilated tubules, loss of glomeruli, hyaline scars, and interstitial sclerosis.

for slight arteriolarsclerosis and faint hyperemia of the nerve heads. Examination made the day before death showed that a few small fresh hemorrhages and early patches of exudate were present. There was no papilledema. Constriction of the arterioles was less marked than that observed in the previous examination.

She complained from time to time of pain in the stomach and moderate rectal bleeding. She was moderately clear mentally up to death. A few days before it she exhibited periods of Cheyne-Stokes respiration and a little dyspnea. An attempt was made to promote urine excretion by means of glucose given intravenously (500 c.c.) with 10 per cent of 95 per cent alcohol added. No diuresis resulted, but the patient had a long restful sleep. One day before death the content of CO_2 in the serum was 13.47 millimols per liter at pH 7.13. The serum chloride was 90.5 milli-equivalents.

During the morning of the day of her death slight fibrillary twitching was observed, but except for nausea she had no complaints.

Autopsy (Dr. C. P. Rhoads), 4–1/2 Hours Postmortem. The findings of especial interest during the gross examination of the body were, absence of pericardial effusion, marked left ventricular hypertrophy (weight 480 grams) and diffuse atherosclerosis of the coronary vessels. In many places the intima of these vessels had become thin and brittle. Throughout the aorta, confluent atherosclerotic patches were present. There was marked emphysema of the lungs. The vessels of the spleen were markedly thickened. The mucous membrane of the stomach and intestine was edematous and deeply injected. Extending from the duodenum to the end of the large intestine there were many areas which were deeply injected, in the center of which were shallow ulcerations (1.0 to 3.0 cm. in diameter) extending through the mucosa and covered with yellow exudate. The sternal bone marrow was pale brick red in color and fairly cellular. No gross abnormality was observed in the brain or pituitary gland.

The left kidney weighed 32 grams and the right 38 grams. Both were markedly reduced in size. The capsules stripped with difficulty leaving an irregular contracted surface. The cortex was 1.0 to 3.0 mm. in width. Branches of the renal artery showed markedly thickened walls.

Microscopic examination showed that marked intimal sclerosis with necrosis and formation of cellular, sclerotic scars was present in the coronary vessels. Most of the vessels in the spleen and liver showed sclerosis. Very striking increase in the number of basophile cells in the anterior lobe of the pituitary gland was present. Chromophobe cells were few in number, while acidophile cells were numerous.

Sections of the kidney (figure 3) showed extremely advanced sclerosis and infiltration of interstitial tissue with lymphocytes. Many glomeruli had disappeared and others were converted into hyaline scar tissue. Others exhibited hyaline thickening of the capillary wall with proliferation of epithelial and endothelial cells, and decrease of intravascular red blood cells. The tubules were atrophied and dilated, many containing a basophilic exudate. The arteries and arterioles presented most marked morbid change. Very marked fibrous intimal thickening was present along with hyaline change of the nuclei, with almost complete occlusion in many instances.

Discussion

Onset of the disease was insidious in character. Gross hematuria, headache, fever and evidence of infection—so characteristic of the acute onset—were lacking. She was not aware that she was ill until swelling of the ankles occurred. By that time the blood pressure was elevated to 200/120 mm. of Hg, indicating, probably, that the morbid process was already of months' or years' standing. It has been the experience in this clinic that those patients in whom the onset is insidious are likely to die usually within a few years, contrasting with those in whom the onset is stormy, many of whom recover completely.

When she was first seen in this clinic she had entered the terminal stage. Van Slyke and his associates [6] define this as the stage during which urea clearance is below 20 per cent of normal and uremia may supervene at any time. Usually it lasts less than a year, but, as this patient illustrates, may continue for 20 months or more.

Physical examination showed that she was in a poor state of nutrition. A diet, liberal both as to calories and protein content, rapidly brought improvement. She was able to maintain good nutrition until within a few weeks of death. Coincident with improvement of nutrition was a feeling of well being. It is our belief that if patients with nephritis are properly nourished they may enjoy life to within weeks or months of death.

Since edema was almost the only symptom of which she complained, it was desirable to rid her of it. Excretion of protein in the urine was not great, but nevertheless she was unable to keep the plasma protein at a normal level, probably due to inability to synthesize them. Edema in this case appeared to be largely due to salt, for if it were withdrawn the edema disappeared, and reappeared on resuming it. A diet containing 100 grams of protein for one month did not cause the plasma proteins to rise, nor did an isocaloric one containing 20 grams fed for 45 days cause them to fall. Again the high protein diet was resumed, this time for five months, without significantly affecting them. Reduction of protein to 30 grams for a period of 4½ months followed, again without effect. Nor was any close relationship found between the level of protein in the diet and excretion of protein in the urine. It appears that in this patient, who was well nourished, protein intake of from 20 to 30 grams covered the amount lost in the urine and the requirements of the tissues, but that even 80 to 100 grams were unable to raise the level of the plasma proteins. It is for this reason that it was our belief that ability to synthesize them was impaired.

Since it was necessary to interdict salt in the diet, an excellent opportunity was afforded to observe the effects of its deprivation. For 19 months she received little more than a gram of it a day. This was controlled by estimation of the salt content of the urine two days of each week. At no time were symptoms referable to its withdrawal evident, nor did the chloride in the serum fall below the lower limits of normal. Since polyuria was not present it appears that she did not wash out sufficient tissue chlorides to cause symptoms of hypochloremia.

Anemia was not marked until shortly before death. It appears to be of significance that the hemoglobin fell slowly. It is often observed that rapid diminution of hemoglobin may be associated with early termination of the patient's life. Large doses of reduced iron did not increase hemoglobin, but following a hemorrhage it appeared to aid in its recovery to the level maintained before the hemorrhage. Hematuria was never sufficient to contribute to the anemia.

The periods of marked hypertension alternating with those during which arterial pressure was nearly normal are of interest. One might well have been deluded into thinking that therapeutic success had been achieved were treatment to have been instituted at a time coincidental with the naturally occurring pressure reduction. Such more or less rhythmic changes recurring within a cycle of weeks or months are not rarely observed in this clinic. Changes in arterial pressure were unaccompanied by changes in renal efficiency as measured by urea clearance.

Morbid changes in the eyegrounds were limited to arteriolar constriction until weeks or days before death, when both exudate and hemorrhages appeared. We believe this to be an especially good prognostic sign. Lack of fundus changes often aids in differentiating the terminal stage of malignant hypertension from that of hemorrhagic nephritis. In the former profound changes may be the presenting symptom from onset of the disease, and always are observed in the terminal stage. Exudation, destruction of vessels, old and new hemorrhages and papilledema characterize these changes. Although similar changes may be observed in the fundi of a nephritic patient, they often follow the course illustrated by this patient. It is then that fundus examination is of differential diagnostic value.

The vascular system of this patient, including the heart, withstood the hypertension well. Although the arterial pressure was often higher than may be observed in cases of malignant hypertension, the heart enlarged slowly and caused but a minimal number of symptoms. The electrocardiograph showed, however, that damage was occurring. Autopsy confirmed the belief that the morbid changes in the blood vessels were extensive. They consisted of sclerosis and deposition of lipids without the hemorrhages into the vessel wall which are so often observed in malignant hypertension.

She suffered from oliguria approaching anuria for 18 days before death. In spite of this and a marked rise in retention products in the blood, there were few classical symptoms of uremia except vomiting. Only on the last few days were occasional fibrillary twitching of the muscles and a little drowsiness observed. It is a matter of surprise that a patient who for 19 months or more had suffered from severely restricted renal efficiency was able to withstand 15 days of almost complete anuria without exhibiting many symptoms or signs. Anuria resulting from a surgical procedure or that occurring during the acute stage of nephritis may end fatally in shorter periods.

Autopsy revealed two facts of interest which are not usual in such cases, and for which we have no explanation. The first was the presence in the anterior lobe of the pituitary gland of an increased number of basophile cells. The second was the absence of pericarditis, either old or fresh.

Summary

A case of terminal hemorrhagic nephritis has been presented to illustrate the elusive nature of the signs and symptoms and their relationship to diagnosis and prognosis. The following points were especially well exemplified:

1. An insidious onset usually means a fatal termination of the disease.
2. The terminal stage (urea clearance less than 20 per cent of normal) may last for many months and at times more than a year.
3. Poor nutrition contributes to the discomfort and ill health of the patient. Good nutrition may spell the difference between well being and invalidism. Protein should be sufficient to cover the needs of the tissues and to replace that lost in the urine. High protein feedings need not restore the plasma protein level to normal, nor low protein diets reduce it. It is assumed that the ability of some patients to synthesize plasma proteins is impaired.
4. Interdiction of salt may abolish edema even though plasma proteins do not rise above the level at which edema may occur. If polyuria does not occur with

washing out of large quantities of tissue chlorides, chloride restriction may be as extreme as little over one gram without producing symptoms of hypochloremia or significantly reducing the chloride in serum.

5. Even when hemoglobin is not markedly reduced, and further reduction is slow, death may occur in uremia. Administration of iron will not affect its level except under certain special circumstances such as hemorrhage, when it appears to aid in regeneration of the lost hemoglobin.

6. Arterial blood pressure may alternate between being markedly elevated for periods of weeks or months and being almost normal. This is peculiarly deceptive when treatment designed to lower blood pressure is being investigated. Associated changes in renal efficiency as measured by urea clearance do not occur.

7. Morbid changes in the eyegrounds other than arteriolar constriction may not be present until weeks or days before death, aiding thus in the differential diagnosis from malignant hypertension in which fundus changes are always advanced in the terminal stage and usually during its onset.

8. Oliguria approaching anuria may last for relatively long periods (18 days) in spite of a preliminary period of severe renal inefficiency without producing marked signs or symptoms.

9. An increased number of basophile cells may be found in the pituitary gland.

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TONSILLITIS ASSOCIATED WITH ACUTE ASEPTIC MENINGITIS *

By David Riesman, M.D., Sc.D., F.A.C.P., *Philadelphia, Pennsylvania*

Case Reports

Case 1. Mr. I. B., a married man of 45 years, a native of New York City, had always enjoyed good health. On Tuesday, April 4, 1933, he awoke with a severe headache and a sore throat. The headache was obstinate, not yielding to codeine

* Read before the Section on Medicine of the College of Physicians of Philadelphia, February 25, 1935; with additions.

or other anodynes. Sinus roentgen-ray and blood Wassermann test were negative. The blood count was entirely normal, the fasting sugar 120 mg. per 100 c.c. of blood. The tendon reflexes were exaggerated on the right side and the Babinski reflex was present on that side. Eye ground examination showed dilated vessels but no papill-edema. Lumbar puncture revealed the following: Pressure 22 mm. of mercury, globulin increased, sugar 55.4 mg., Wassermann and colloidal gold tests negative. The cell count was surprising—there were 1125 cells to the cubic mm. The fluid was sterile on culture.

I had the opportunity of seeing Mr. B. with his physicians, Drs. Goodheart and Ginsburg, on April 9. The notes of the result of my examination are as follows:

The patient looks ill and is exceedingly apprehensive, perhaps because of the persistent headache, perhaps because of the many examinations and tests which the obscurity of his illness has rendered necessary. The headache is apparently very severe and he is inclined to dig his head into the pillow. The pupils are slightly unequal, markedly contracted but react to light; all ocular movements are normal. The tongue is covered with a thick white coating. Over the right tonsil a whitish exudate is visible like that of follicular tonsillitis; the left tonsil cannot be seen satisfactorily. The heart and lungs are normal. The liver is a little enlarged, the abdomen slightly distended, the suprapubic region dull on percussion; the spleen is not palpable. The knee jerk is normal, the Babinski reflex is absent, but there is a suggestion of an ankle clonus on both sides. While there is no real ataxia of the arms, the tips of the fingers are not easily brought together. The knee-heel test is normal. There is no rigidity of the neck, no Kernig sign. The eye grounds are normal. The temperature is 102 to 104°; blood pressure 122 systolic, 70 diastolic; the pulse ranges from 70 to 90, respiration 20. The leukocytes in the blood are 16000 per cubic mm.

On questioning the patient I obtained information about an incident that may have had considerable bearing upon his case. On April 1, three days before the onset of the illness, he had been unexpectedly called to the home of an aged uncle. When he arrived he found his relative lying dead on the floor. It was the first death he had ever seen and the shock was, as he expressed it, terrible. It would not seem to be an unwarranted assumption that this psychic trauma had something to do with the localization of the poison in the cerebral meninges.

I was of the opinion that the tonsillitis was the primary element in Mr. B.'s case and that with its subsidence the meningitic symptoms would also disappear. As a therapeutic measure I advised the application of leeches to the mastoid processes. Recovery was rapid, the patient leaving the hospital on April 14. On April 27 he came to see me in my office in Philadelphia. He felt fairly well but still had some ringing in the ears, a feeling of a "kink" in the back of the neck and occasionally weak spells, relieved by lying down. He was nervous, irritable and easily upset. Physical examination revealed nothing of significance except a momentary ankle clonus on both sides but no Babinski reflex. I have heard of the patient since then. He is entirely well.

Case 2. The second case occurred at the Children's Hospital in the service of Dr. Joseph Stokes, through whose courtesy I am privileged to include it in this report. The patient was a boy of four years, of Italian parentage, who apparently as the result of some birth injury had had convulsions up to the age of three years. They then ceased and the child was subjectively normal until one day in May 1933, when he suddenly became feverish and had a convulsion. His breathing was of the Biot type; temperature 102. The limbs were alternately rigid and relaxed; the Babinski reflex was present on both sides, no Kernig sign; some rigidity of the neck. Examination of the throat showed a slight degree of tonsillitis. Spinal puncture yielded a somewhat opalescent fluid; pressure 18 mm. of mercury, globulin increased, sugar present, 500 cells to the cubic mm.; nearly all were lymphocytes. After the spinal puncture the child had no further convulsions. A second puncture showed 1000 cells,

chiefly lymphocytes. There was no pellicle, and no organisms were found. Blood culture showed *Streptococcus viridans;* the Wassermann test was negative. The child's temperature became normal and the cell count in the spinal fluid was reduced to 10. A second blood culture again showed a profuse growth of *Streptococcus viridans,* but a third taken five days later was negative.

The diagnosis in this little boy was obscure but Dr. Stokes and his colleagues concluded that he had had a sterile meningitis, streptococcus tonsillitis and *Streptococcus viridans* septicemia without endocarditis. The child made a satisfactory recovery.

I am prompted to report these two cases because they illustrate certain unusual complications of acute tonsillitis. Although I did not see the first patient in the beginning nor the second one at any time, I believe the conclusion is justified that the tonsillitis was the primary disease.

The promptness of the recovery of both patients is unusual and puts this type of meningitis in a class by itself.

The literature is very meager on the subject of tonsillitis and meningitis. Kroll [1] is the only author among the many I have consulted who speaks of tonsillitis (angina) as a possible cause of acute serous meningitis. Cases of septic meningitis following tonsillitis, usually of the quinsy type, are recorded. There are also references in the literature to encephalitis complicating tonsillitis. Fanny Halpern reported six cases, all in the female sex, of pontine-cerebellar encephalitis in persons ranging from 11 to 60 years. Halpern was unable to determine whether the inflammation of the brain was due to organisms or toxins of the tonsillitis or to a lessening of resistance to the encephalitis virus produced by the tonsillar infection. It must be remembered that the differential diagnosis of meningitis and encephalitis is sometimes difficult.

That there was a definite meningeal involvement in both the cases here reported cannot be doubted in view of a spinal fluid cell count of 1000 in one and 1100 in the other. As the fluid was sterile, I was inclined to the opinion that a virus might have been responsible, although the action of a bacterial toxin could not be ruled out. The fact that the cases were "aseptic" brings them in line with a number of similar ones recorded within the last few years—those of Wallgren,[2] under the title of "Meningitis 'Aseptica' Acuta," of Viets and Watts,[3] as "Aseptic (Lymphocytic) Meningitis" and of Dickens,[4] under the same title. Dickens in his article asks the question whether he was dealing with "a new disease entity due to a filterable or nonfilterable virus." In 1934 Armstrong and Lillie [5] called attention to a virus they had encountered in monkeys which had shown definite signs and symptoms of meningitis; mice and guinea-pigs proved also to be susceptible to the virus. In May of this year Rivers and Scott [6] reported the isolation of a virus from two human cases of meningitis, and stated that the serum from these cases protected animals from the virus. Crossed serological tests indicate the identity of the two viruses, that of Armstrong and that of Rivers and Scott.*

Armstrong and Dickens †[7] in four human cases of "aseptic" meningitis found that the blood serum obtained in one case three years and eleven months,

* The Armstrong-Rivers and Scott virus appears by serologic tests to be identical with a third virus, that of Traub, found in white mice.

† I want to express my thanks to Lieutenant Commander Dickens and to Dr. Charles Armstrong of the Public Health Service for letting me have a manuscript copy of their forthcoming article.

in one a year, in one three and a half years after the attack protected mice against the Armstrong virus. In the fourth case protective bodies were absent at the beginning of the illness, but appeared two months after the onset of the meningitis.

The clinical picture in these cases was similar to that of I.B. except that in the cases recorded by Dickens and Armstrong infections of the upper respiratory tract and not a well-defined tonsillitis preceded the onset of meningeal symptoms. The disease lasted from ten days to two weeks and left no residual features of any kind. In all these cases the cellular response of the spinal fluid was almost entirely lymphocytic. It is easy to see how such a cytologic finding might suggest the diagnosis of tuberculous meningitis. There is, however, no pellicle, and animal inoculation is negative. The sugar, chloride and urea content of the fluid is within normal range.

As far as our present knowledge goes the disease is self-limited and requires little treatment except lumbar puncture which is the best means of controlling the most distressing symptom, the headache. As an adjunct to or substitute for lumbar puncture, leeching from the mastoid process may be tried.

It is desirable that those who hereafter see cases of aseptic meningitis * have laboratory tests made with the spinal fluid for the discovery of a possible virus, and with the blood serum which in the virus cases ought to protect mice against the virus.

Meningeal symptoms are not rare in the acute infections of childhood and also in pneumonia. These symptoms are often attributed to meningism, whatever that may mean. If lumbar puncture is done in such cases, it may reveal a pleocytosis suggestive of acute lymphocytic meningitis.†

In conclusion I should like to say that as far as tonsillitis is concerned, experience has long ago convinced me that it is a potentially serious disease and should be treated with more respect than is customary.

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* Armstrong and Dickens state that since in their opinion the affection is caused by a virus, "aseptic" is a misnomer and propose the term "acute lymphocytic choriomeningitis."

† Pleocytosis has been found in typhoid fever (Dr. James P. Leake—personal communication).

INTERMITTENT HYDRARTHROSIS ASSOCIATED WITH UNDULANT FEVER *

By JOHN C. SHARPE, M.D., *Omaha, Nebraska*

ARTHRALGIA has long been recognized as part of the symptom-complex of undulant fever. However, true arthritic changes associated with the disease have not been emphasized as a predominant feature. We have had the opportunity in the past few years to see several such cases, which form the basis of another paper [1] dealing with these rheumatic manifestations.

The following case is of sufficient rarity and interest to warrant its individual consideration.

CASE REPORT

History. J. F., 25, white, male, grocery clerk, entered the University Hospital on December 12, 1934, complaining chiefly of pain and swelling of the knees. The family and past history were non-contributory. He had always enjoyed excellent health until the onset of the present illness five years before admission. At that time he had first noted pain and swelling of both knees, the right ankle and the right wrist joint which persisted for six weeks. During the following year, the pain and swelling of the knees came and went at irregular intervals. On two occasions aspiration of fluid from these joints was required for the relief of pain. He was not aware of any associated fever at that time. One year before entrance to the hospital, the pain and swelling of the knees returned and again required several aspirations of the joints for the relief of pain. From that time to the present, he had noted a definite intermittent character of the swelling. He had been aware of an evening rise of temperature, at times reaching 102°. He had had little or no appetite and had lost 20 pounds in weight. As the result of his difficulty in walking, he had been unable to work. Additional history revealed the facts that at the time of the onset of the first arthritic symptoms, he had lived on a farm in Nebraska where he had drunk raw cow's milk, and that there had been several instances of abortion in cattle on nearby farms.

Physical Examination. Examination revealed a well developed but poorly nourished young man with a moderate pallor of the face and mucous membranes. The temperature was 100.4°, the pulse 90, the respirations 20, and the weight 117 pounds. The blood pressure was 120 systolic, and 70 diastolic. There was a suggestive bilateral exophthalmos. The tonsils were small and adherent. There was a moderate generalized lymphadenopathy present, especially of the axillary nodes. The thyroid was not enlarged. The lungs were clear to percussion and auscultation. The heart was not enlarged. The first sound at the apex was accentuated, followed by a short systolic murmur. The splenic tip was palpable 2 cm. below the left costal margin. The liver was not enlarged. Examination of the joints showed some stiffness of the left elbow and some swelling of the right ankle. There was bilateral swelling of the knees (figure 1), the right measuring 37.5 cm., the left 35.5 cm. in circumference. There was a definite patellar ballottement, a moderate limitation of motion and no local hyperemia of the overlying skin. The patient complained of pain in the knees only at the time the swelling reached its highest level. The remarkable feature of the case was the periodicity of the swelling which occurred at the same time in both knees, in seven to ten day cycles. The measurements of their circumferences varied from 0.5 cm. to 6.0 cm. During the period of recession, the swelling never entirely

* Received for publication July 19, 1935.

From the Department of Medicine, University of Nebraska, College of Medicine, Omaha, Nebr.

FIG. 1.

disappeared from the right knee but occasionally did so on the left side. During the diagnostic study and progress of the case, daily noon-day measurements were recorded (figure 2).

Laboratory Examinations. The blood showed a hemoglobin of 52 per cent, erythrocytes 3,440,000, leukocytes 5,000. The differential cell count was normal. The smear showed moderate anisocytosis and poikilocytosis. The bleeding and coagulation time were normal. The urine was normal, Wassermann reaction negative. The blood chemistry was normal. The basal metabolic rate was + 18. Roentgenograms of the knees (figure 3) were interpreted as showing rheumatoid arthritis of moderate degree. Agglutination with the Brucella group, by the Huddleston technic, was found to be postive in a dilution of 1–400. Repeated cultures of the blood, urine and synovial fluid for *Brucella abortus* and *melitensis* were negative after three weeks. The cultures were made on blood plates, brain broth, liver infusion. Duplicate cultures on the latter medium were incubated in an atmosphere containing CO_2. A direct smear of the synovial fluid sediment showed many segmented neutrophiles, but no bacteria could be observed.

Course. The temperature was usually normal in the morning but would rise as high as 101° to 103° during the evening, usually accompanied by profuse sweating, occasionally chills. The increasing doses of undulant fever vaccine (Lederle), administered subcutaneously, caused little or no appreciable effect on either the dramatic, intermittent swelling of the knees or the nocturnal rise of temperature. He was discharged from the hospital January 28, 1935, and then followed in the out-patient department where vaccine therapy was continued at bi-weekly intervals until a total

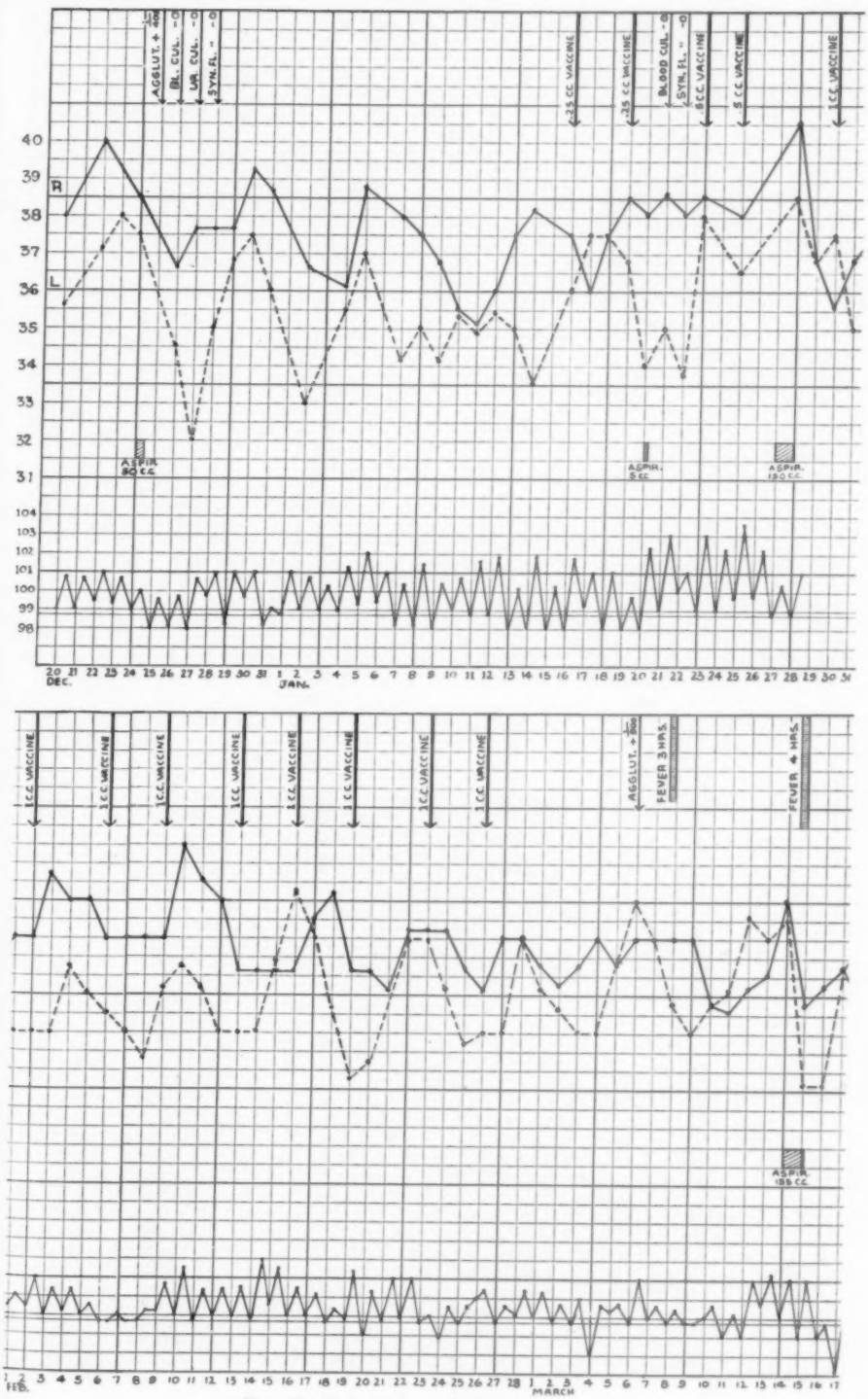

FIG. 2. Intermittent Hydrarthrosis.

(*Continued on next page.*)

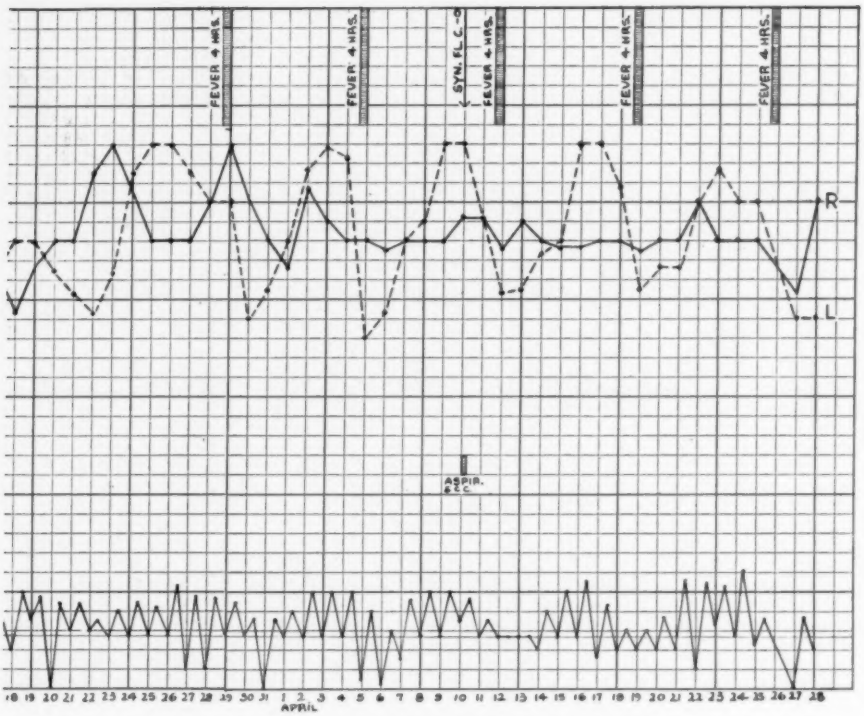

FIG. 2. Intermittent Hydrarthrosis.

FIG. 3.

of 10 c.c. had been given. At the end of this time, there appeared to be slight but definite decrease in the fluctuations of the swelling of the knees, a moderate decrease in the evening temperature and an improvement in his general strength.

Further Course. At the suggestion and under the direction of Dr. A. E. Bennett, Lutheran Hospital, Omaha, the patient was given a course of fever therapy by means of a Kettering hot air cabinet. Each weekly treatment consisted of raising the patient's temperature to 105° to 106° and maintaining it for four hours. During the first four weeks, the size of the knees varied widely, but after the fourth treatment the right knee remained approximately uniform in size, moderately swollen. The left knee continued the periodic swelling every six to eight days. The patient ceased to complain of pain in the knees, and there was less limitation of motion. There had also been a gain of eight pounds in weight. However, the evening rise of temperature continued, there was no improvement in the anemia, and the enlargement of the lymph nodes persisted as well as the splenomegaly. The agglutination reaction remained positive in dilutions of 1–500. Continued attempts to cultivate organisms from the synovial fluid were unsuccessful.

Comment

Because of our patient's loss of weight, the perspiration, the tachycardia, the moderate bilateral exophthalmos and the moderately increased basal metabolic rate, an associated hyperthyroidism was at first considered. Curtis [2] reports a patient with undulant fever complicating toxic goiter who improved greatly following operation. He emphasized the similarity of the symptoms of the two diseases. We have also seen such a case that improved following operation.

Up to the present time, there has been only one previous report of intermittent hydrarthrosis of the knees definitely proved to be due to Brucella. This case was reported by Baker [3] in 1929 at the Johns Hopkins Hospital. His patient was a 47 year old Virginia man who, while slaughtering hogs, after an exposure to cold developed periodic swellings of both knees that continued for several months. The swellings were found to alternate precisely in seven day cycles. Although the agglutination reaction of the blood was at first negative, *Brucella abortus* was cultivated from the synovial fluid of both knees, the blood and the urine. Vaccine therapy was effective in reducing both the nocturnal temperature and the swelling of the knees, but only while the patient remained in the hospital. The hydrarthrosis reappeared when he returned to work which necessitated standing. Our case showed only moderate improvement following vaccine therapy and further slight improvement after seven fever treatments.

Baker suggested that infection by a member of the Brucella group of organisms might prove to be the cause of the interesting and rare clinical syndrome, intermittent hydrarthrosis. With this in mind we studied our patient, and while we were not able to prove definitely that the hydrarthrosis was due to *Brucella abortus* or *melitensis,* there was little doubt that our patient presented an active and persistent case of undulant fever. We are in accord with Baker in stating that because of the lack of uniformity of opinion regarding the etiology of intermittent hydrarthrosis and since many of the recorded cases give a history of " fever " simulating malaria and finally because two cases of undulant fever have now been reported associated with intermittent hydrarthrosis, further attempts to determine the relationship of the two conditions should be made.

SUMMARY

1. A second case of undulant fever associated with intermittent hydrarthrosis of the knees is reported. The history is of several years' duration.

2. Repeated attempts to cultivate *Brucella abortus* or *melitensis* from the synovial fluid, the blood and the urine were unsuccessful.

3. Only slight improvement followed courses of vaccine and fever therapy.

4. It is hoped that further studies will be made to determine whether a constant relationship exists between Brucellosis and intermittent hydrarthrosis.

Addendum: During the past 10 months, the patient's general condition has been unimproved. In spite of large doses of vaccine, a course of neoarsphenamine, and vigorous symptomatic treatment, the temperature continues its nocturnal rise accompanied by drenching sweats. The wrists, ankles and hip joints have become involved with pain and varying degrees of swelling. The knees continue their intermittent hydrarthrosis. The general lymphadenopathy and splenomegaly are the same, but the anemia and weight loss have become more marked. Repeated agglutinations with *Brucella melitensis* remain positive in high dilutions, but cultures of blood and synovial fluid are persistently sterile.

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EDITORIAL

STUDIES ON INSULIN

EVER since its discovery almost fifteen years ago, many attempts have been made to render insulin still more effective as a clinical agent in the treatment of diabetes. These have taken two general directions: one, to find a more convenient and less difficult method of administration; and the other, to enhance its potency and to prolong the period of its physiological action. The chemical nature of this hormone, with its protein-like structure, probably renders it dependent for its physiological effects upon the molecular arrangement of its seven characteristic amino-acids. This structure also makes it vulnerable to attack by the digestive juices, so that it is unlikely that its oral administration in the present form can ever be effective. It has, indeed, been shown repeatedly that the administration of relatively huge doses of insulin by mouth will produce an irregular hypoglycemia. Some of the hormone under such circumstances is probably absorbed before it can be destroyed, but the effects upon the blood sugar are relatively so slight and inconstant as to make this method quite hopeless as a practical measure. The same objections apply to various devices employed to inactivate the digestive juices temporarily, as by alkalinization, by ingestion with alcohol, by the use of anti-enzymatic preparations, or by coating the insulin with enzyme resistant materials.

Reports of many efforts directed toward the utilization of other routes of administration may be found in the literature. All eventually have been abandoned because of the uncertainty and lack of precision of the results. The quantity required for any effective action is generally several or many times larger than that required by the subcutaneous route. Rectal applications, insufflation into the naso-pharynx, instillation into the external ear, and even into the conjunctival sac, have been attempted. The writer has recently collected no less than fifteen articles which describe efforts to give insulin by skin inunctions. An inconstant effect does seem to be possible with very large doses. A communication has recently appeared reporting promising results by intranasal spray. The history of these studies is always the same. A first enthusiastic report is followed by disappoint-

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ment as the author discovers the impossibility of obtaining the precision and dependability of action indispensable for clinical use.

Nevertheless, the cumbersomeness, inconvenience and pain of the constant hypodermic injections of insulin render any improvement highly desirable. The occurrence of fatty tumors, often disfiguring, as a result of neglect to rotate the site of subcutaneous injections is not so serious a problem as is that of the curious areas of atrophy which are seen from time to time, and which appear to be permanent scars. When one comes to consider the enormous number of hypodermic injections of insulin daily administered by untrained and often careless and dirty individuals, into diabetic tissues which are particularly susceptible to infection, the relative rarity of this complication or of any other is truly remarkable. In the course of ten years a diabetic patient who takes insulin twice daily will receive over seven thousand hypodermic injections.

A more promising line of attack has been that directed toward delaying and enhancing the hypoglycemic action of insulin. If its physiological effect is analogous to that of an enzyme, and current evidence perhaps points in this direction, such investigations may well be considered hopeful and probably eventually fruitful. Injections with various agents which delay absorption by physical means or otherwise have been extensively studied. Mechanical mixture, either of dissolved insulin, or of dry insulin powder, with semi-solid fats or oils, which are themselves absorbed slowly, or with lecithin or cholesterol, or with gum arabic or allied compounds, have not yielded very satisfactory results. Recently Clausen has reported favorable effects with mixtures of adrenalin and insulin. Promising studies upon the enhancement of insulin action by means of combination with protein precipitants, or adsorbents, as metallic salts, particularly those of iron and zinc, have recently been published by Bishoff and Maxwell, and by Scott and Fisher.

Great interest has been aroused in the report of the use of a combination of the protamines derived from the testes of certain species of fish, with insulin hydrochloride, by Hagedorn and his coworkers. These protamines, first extensively studied by Kossel, may form a loose chemical combination with insulin, perhaps analogous to that presented by aniline hydrochloride. The clinical use of this material causes an undoubted prolongation of the usual insulin effect, up to eight or ten hours. The most striking clinical

Scott, D. A., and Fisher, A. M.: Prolongation of insulin action by protamine and zinc, Proc. Soc. Biol. Chem., 1936, lxxxviii.

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result so far noted, aside from its influence upon the hyperglycemia and glycosuria, is the reduction of the liver enlargement sometimes observed in cases of poorly regulated diabetes especially in children. Unfortunately, the preparation of the material for injection, and its stability, present certain difficulties and render it impractical for use on an extensive scale in its present form. A flocculent precipitate is formed, and it is necessary to inject this material in an even suspension. The occurrence of insulin reactions is also somewhat disturbing, in the writer's experience. These come on, as a rule, more slowly and insidiously than do those seen with ordinary insulin, so that the danger involved in failure of recognition is possibly greater. Sweating and hunger are much less marked and the occurrence of rather severe headache is quite common.

There is no doubt that further progress along similar lines in order to secure delayed insulin action will now be rapid. It is of interest, as found in determinations of the molecular weight of insulin by the ultracentrifuge method in Svedberg's laboratory, that significant changes occur with variation in the pH value of the solution. Whereas the insulin molecule is relatively stable within the range pH 4.5 to 7.0 (molecular weight about 35,000), outside this range it dissociates into products of smaller size. This dissociation, however, is reversible. It is possible that the greatly enhanced surface area presented by the smaller dissociated particles increases their adsorption on the tissues and hence slows up their physiological utilization, as compared to that of the ordinary insulin molecule. Important developments of practical clinical value in this field may shortly be expected with considerable confidence.

G. A. H.

REVIEWS

Physical Diagnosis. By RICHARD C. CABOT, M.D. 11th Edition. 540 pages; 16.5 × 23.5 cm. Williams and Wilkins, Baltimore. 1934.

This is the eleventh edition of this deservedly popular textbook. As usual it is notable for the clarity and force with which the material is presented. The well chosen illustrations are a distinct addition to the text. There have been new additions to and enlargements of certain sections, for example those dealing with coronary disease, latent tuberculosis, neoplasms of the lungs and bronchi and the peumonokonioses. The new edition all in all is a further improvement on those preceding it and will no doubt be equally well received.

M. C. P.

Three Philosophers (Lavoisier, Priestley and Cavendish). By W. R. AYKROYD 227 pages; 13 × 21 cm. William Heineman Ltd., London. 1935. 10/6 net.

Historians of medical science often are too concerned with relatively unimportant personal attributes and experiences of the great figures of medicine and too little with their ideas or their contributions. Often too they have more of the bibliophile's interest in the publications that have changed the course of scientific progress than that of the student of science. The present little volume seems to the reviewer a model of its kind. The author writes charmingly of the lives of three great scientists and of the period in which they lived. It is evident that he is thoroughly at home in the history of the late eighteenth century. On this background he develops very clearly and interestingly the story of how each contributed to our present knowledge of the composition of water and air. The significance of Lavoisier's metabolic investigations is well brought out. Toward the end of the volume the later life and death of the three philosophers is well told. To most readers the material especially on the life of Lavoisier will be new. It is a small volume which will be read by any physician with interest and profit.

M. C. P.

Medical Tactics and Logistics. By COLONEL GUSTAVUS M. BLECH, M.C., U. S. A., and COLONEL CHARLES LYNCH, M.C., U. S. A., Ret. 201 pages; 15.5 × 23.5 cm. Charles C. Thomas, Springfield, Ill. 1934. Price, $4.00.

The authors have written this book to afford "medical officers, patriotic physicians and medical students a fundamental idea of the nature of their duties in the event of a national emergency." It begins with a number of short chapters on "Theory Development and Principles of War" and then proceeds to recount in considerable detail the military and medical aspects of an imaginary war, or succession of skirmishes about the borders of Maryland and Pennsylvania. All the moves in this conflict are discussed pro and con at some length and a conscientious effort is made to drive home certain elementary lessons. A folder of maps of the region accompanies the volume.

In this war everything proceeded according to regulations. Apparently orders were issued constantly and obeyed promptly, liaison was perfect, everyone knew all he should know about what was going on, maps must have been issued in abundance and medical supplies were never seriously lacking. The behavior of almost everyone was exemplary. The reviewer hopes that the next war will resemble the one here described.

Those who took part as regimental medical officers in the forward areas in the past war will find most of this volume highly theoretical and unreal. However,

there is a foundation of sound doctrine in it, and its perusal will give the battalion surgeon of the future a good general notion of how the medical corps at the front is intended to function. Following this he would do well to read "The Lost Legion" or "Chevrons" to get a more realistic conception of what a war is like.

M. C. P.

Disorders of the Blood. By LIONEL E. H. WHITBY and C. J. C. BRITTON. 543 pages; 16 × 24 cm. P. Blakiston's Son and Co., Inc., Philadelphia. 1935.

The authors have produced a book which may be recommended unreservedly to the attention of all physicians engaged in the practice of internal medicine. It meets in a very adequate way the need for a monograph in which the large and scattered literature of hematology of the last ten years is gathered together, added to our basic knowledge of the subject and presented as a whole. The earlier chapters deal with the origin, functions and fate of blood cells, the abnormalities of hemopoiesis, and the methods of study and of differentiation of the various formed elements of the blood. Then comes, in several chapters, an excellent discussion of the anemias. The first and second of these chapters deal with the causes of anemia and with the principles of treatment. It would be hard to find elsewhere as compact, as clearly stated and as interesting a discussion of our more recent knowledge of these topics. In the later chapters on the various types of anemia the chapter on pernicious anemia and that on anemias due to disease of the alimentary tract are of particular interest. The anemias of infancy and childhood receive notice in a separate chapter.

The purpuric and hemorrhagic states are discussed rather briefly though even rare forms are mentioned. In the chapter on aplastic diseases the data on agranulocytic angina are derived almost wholly from American sources, and there is very little expression of the authors' own opinions.

The leukemias, affections of the spleen, the blood changes in infection and infectious diseases and in miscellaneous conditions occupy the latter half of the book. Blood groups and blood transfusion are discussed.

The book is well organized and carefully written. There is a good index. References are placed at the end of the chapters. The tables, illustrations and colored plates are helpful.

The treatment of such a large field is necessarily brief, and it is perhaps inevitable that the tone should be at times dogmatic. A more critical evaluation of proposed therapeutic measures would be helpful in some sections. All in all, however, this is a very valuable book. It may be used as a reference or read through with profit as an account of the present status of knowledge concerning disorders of the blood.

M. C. P.

Diseases of the Liver, Gall Bladder, Ducts and Pancreas. By SAMUEL WEISS, M.D., F.A.C.P. 1099 pages; 18 × 26.5 cm. Paul B. Hoeber, Inc., New York. 1935. Price, $10.00.

This large, handsomely printed and illustrated volume is disappointing when put to the test of practical use as a reference volume. It is essentially a compilation of abstracts from the literature. There is a striking lack of orderly and logical sequence in the topical discussions so that the reader is left confused and unsatisfied. Important facts are often stated very briefly or omitted while pages are given to comparatively trivial details. Numerous inaccuracies further detract from the value of the book.

M. C. P.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the following gifts of publications by members to the College Library:

Dr. William C. Boeck (Fellow), Los Angeles, Calif.—1 reprint;
Dr. Vincent W. Koch (Fellow), Janesville, Wis.—1 reprint;
Dr. M. B. Marcellus (Fellow), San Francisco, Calif.—1 reprint;
Dr. Walter M. Simpson (Fellow), Dayton, Ohio—1 reprint.

Committee on Future Policy for the Development of Internal Medicine

Minutes of the Board of Regents, March 6, 1936: "RESOLVED, that a Committee on Future Policy for the Development of Internal Medicine be appointed by the President for the purpose of considering a program of possibilities for using surplus funds for the advancement of Internal Medicine. This Committee shall take under consideration all matters outside that of the College Headquarters, such as fellowships, awards, postgraduate education, initiation fees of new Fellows, revolving funds for the aid of research, etc."

The personnel of this Committee, as appointed by the President, Dr. Ernest B. Bradley, is as follows:

James Alex. Miller, *Chairman*, New York, N. Y.
Walter L. Bierring, Des Moines, Iowa
Roger I. Lee, Boston, Mass.
Maurice C. Pincoffs, Baltimore, Md.
Francis M. Pottenger, Monrovia, Calif.

Dr. George Bachmann (Fellow), Atlanta, Ga., presented a paper on "The Gaseous Metabolism of Glucose, Fructose and a Mixture of These Two Sugars, together with Urinary Findings" at the February meeting of the Dugas Club of the University of Georgia School of Medicine.

The Second Annual Postgraduate Course, "Neuropsychiatry in General Practice," given by the Staff of the Menninger Clinic, Topeka, Kans., will extend from April 20 to April 25. Dr. William C. Menninger (Fellow) and Dr. Ralph M. Fellows (Fellow) are among those contributing to the course.

Dr. Clayton W. Greene (Fellow), Buffalo, N. Y., has been appointed a member of the New York Public Health Council by Governor Lehman.

Dr. George W. McCoy (Fellow), of the U. S. Public Health Service, has been appointed professorial lecturer in preventive medicine at George Washington University School of Medicine.

Dr. Arthur C. Christie (Fellow), Washington, D. C., has been reëlected President of the Board of Trustees of the American University.

Dr. Archibald Barklie Coulter (Associate), Washington, D. C., has been appointed Director of the Bureau of Tuberculosis of the Health Department of the District of Columbia.

Dr. Frank R. Menne (Fellow), Portland, Ore., and Dr. Delbert H. Nickson (Fellow), Seattle, Wash., have been elected President and Vice-President, respectively, of the recently organized Pacific Northwest Society of Pathologists.

Brig. Gen. Matthew A. Delaney (Fellow), Assistant to the Surgeon General, U. S. Army, has retired on his own application. General Delaney graduated from the University of Pennsylvania in 1898. He also held the Certificate of Public Health from Harvard University School of Medicine. He has been in the Medical Corps of the U. S. Army since 1901, and is retiring at the age of sixty-one. He was White House physician during the administration of President Taft from 1909 to 1913. Earlier he served in the Philippines and during the World War, he was in charge of Base Hospital No. 10, and was later detailed as liaison officer with the British War Office. He received the Distinguished Service Medal, and was decorated by the British Government.

Dr. Joseph C. Doane (Fellow), Medical Director of the Jewish Hospital, Philadelphia, and Dr. Martha Tracy (Fellow), Dean of the Woman's Medical College of Pennsylvania, have been appointed to the Philadelphia Board of Health, to succeed Dr. James M. Anders (Master), resigned, and the late Dr. Ellwood R. Kirby.

Dr. William B. Castle (Fellow), Associate Professor of Medicine at Harvard University Medical School, received the Procter Award on the occasion of "Professional Day" of the Philadelphia College of Pharmacy and Science, January 31.

Dr. Charles A. Doan (Fellow), Professor of Medicine and Director of Research, Ohio State University College of Medicine, Columbus, delivered the Beaumont Lectures for 1936, sponsored by the Wayne County (Mich.) Medical Society, March 23 to 24. The lectures were given on "The Histopathology of the Blood."

The Scientific Assembly of the American Medical Association decided in December to have an afternoon session at the coming meeting in Kansas City in May devoted to Tuberculosis, under the Section on Miscellaneous Topics. The officers appointed for this Session were Dr. James Alexander Miller (Fellow), New York City, Chairman; Dr. Charles Hartwell Cocke (Fellow), Asheville, N. C., Secretary.

The Session is to be held Wednesday afternoon, May 13; and the preliminary program will include, in addition to the Chairman's Address, papers by Drs. Max Pinner, Oneonta, N. Y.; J. Burns Amberson, Jr., New York City; LeRoy S. Peters, Albuquerque, New Mex.; and J. J. Singer, St. Louis, Mo., all members of the College.

Elections to Fellowship

March 1, 1936

Candidates	*Sponsors*
	Alabama
Joseph E. Hirsh, Birmingham:	James S. McLester, Charles H. Cocke, Fred W. Wilkerson.
	Arizona
Benson Bloom, Tucson:	Allen K. Krause, Charles W. Mills, W. Warner Watkins.
	Arkansas
Francis Joseph Scully, Hot Springs:	Arthur G. Sullivan, D. C. Lee, Oliver C. Melson.
	California
Harold Milton Walton, Loma Linda:	G. Stirling Landon, Roland Cummings, F. M. Pottenger, James F. Churchill.
Clarence Emory Johnson, Long Beach:	Samuel M. Alter, Noel F. Shambaugh, F. M. Pottenger, James F. Churchill.
Ernest Mosiah Hall, Los Angeles:	Roy E. Thomas, Egerton Crispin, F. M. Pottenger, James F. Churchill.
Cullen Ward Irish, Los Angeles:	John V. Barrow, Samuel D. Ingham, F. M. Pottenger, James F. Churchill.
Orlyn Bernard Pratt, Los Angeles:	Percy T. Magan, Newton Evans, F. M. Pottenger, James F. Churchill.
Harold Guyon Trimble, Oakland:	George H. Evans, Chesley Bush, F. M. Pottenger, Hans Lisser.
Mark Gerstle, Jr., San Francisco:	Dudley W. Bennett, H. Clare Shepardson, Hans Lisser.
	Connecticut
W. Bradford Walker, Cornwall:	Charles H. Turkington, George Blumer, Henry F. Stoll.
Wilmar Mason Allen, Hartford:	Otto G. Wiedman, James E. Hutchison, Henry F. Stoll.
Wilmot Charles Townsend, Hartford:	G. Gardiner Russell, Otto G. Wiedman, Henry F. Stoll.
Benedict Richard Harris, New Haven:	George Blumer, C. J. Bartlett, Henry F. Stoll.
Max Harold Ruby, Waterbury:	John H. Foster, J. Harold Root, Henry F. Stoll.
	Delaware
Joseph Marion Messick, Wilmington:	George H. Gehrmann, Olin S. Allen, Lewis B. Flinn.
Edgar Raymond Miller, Wilmington:	Olin S. Allen, Bartholomew M. Allen, Lewis B. Flinn.
	Medical Corps, U. S. Army
Frank R. Borden, Randolph Field, Tex.:	Charles R. Reynolds.
Thomas Ward Burnett, Salt Lake City, Utah:	Charles R. Reynolds.
George Clark Dunham, Washington, D. C.:	Charles R. Reynolds.
George Martin Edwards, Fort Sam Houston, Tex.:	Charles R. Reynolds.
Robert M. Hardaway, Denver, Colo.:	Everett L. Cook, William C. Pollock, Charles R. Reynolds.

Candidates	*Sponsors*
Arthur Parker Hitchens, Washington, D. C.:	Charles R. Reynolds.
Glenn I. Jones, San Rafael, Calif.:	Charles R. Reynolds.
John G. Knauer, Denver, Colo.	Charles R. Reynolds.
George F. Lull, Washington, D. C.:	Charles R. Reynolds.
Harry D. Offutt, Honolulu, T. H.:	Charles R. Reynolds.
Henry Church Pillsbury, Washington, D. C.:	Charles R. Reynolds.
Charles G. Sinclair, Fort Sam Houston, Tex.:	Charles R. Reynolds.
MEDICAL CORPS, U. S. NAVY	
John Ryer Poppen, San Pedro, Calif.:	Perceval S. Rossiter.
George Washington Taylor, Louisville, Ky.:	Oscar O. Miller, E. R. Gernet, Perceval S. Rossiter.
DISTRICT OF COLUMBIA	
Clapham Price King, Washington:	William Earl Clark, E. Clarence Rice, Wallace M. Yater.
ILLINOIS	
Thomas J. Coogan, Chicago:	George W. Hall, George H. Coleman, Arthur R. Elliott, James G. Carr.
George B. Stericker, Springfield:	Cecil M. Jack, D. O. N. Lindberg, Samuel E. Munson.
INDIANA	
James Oscar Ritchey, Indianapolis:	John A. MacDonald, Edgar F. Kiser, Robert M. Moore.
IOWA	
James Stuart McQuiston, Cedar Rapids:	Herbert W. Rathe, Elmer G. Senty, Walter L. Bierring, Tom B. Throckmorton.
Benjamin Franklin Wolverton, Cedar Rapids:	John H. Peck, Elmer E. Kottke, Walter L. Bierring, Tom B. Throckmorton.
William Edward Ash, Council Bluffs:	Ernest Kelley, Aldis A. Johnson, Walter L. Bierring, Tom B. Throckmorton.
John Calvin Parsons, Creston:	John H. Peck, Daniel J. Glomset, Walter L. Bierring, Tom B. Throckmorton.
Martin Ingeman Olsen, Des Moines:	Daniel J. Glomset, Addison C. Page, Tom B. Throckmorton.
Edwin Basom Winnett, Des Moines:	John H. Peck, Daniel J. Glomset, Walter L. Bierring, Tom B. Throckmorton.
KANSAS	
Ralph Mason Fellows, Topeka:	William C. Menninger, Howard E. Marchbanks, Thomas T. Holt.
KENTUCKY	
Samuel Spafford Ackerly, Louisville:	John Walker Moore, William E. Gardner, Chauncey W. Dowden.
MAINE	
Henry Myer Tabachnick, Portland:	Eugene H. Drake, Elton R. Blaisdell, Edwin W. Gehring.

Candidates	*Sponsors*
	MARYLAND
Paul W. Clough, Baltimore:	Thomas P. Sprunt, George A. Harrop, Henry M. Thomas, Jr.
William S. Love, Jr., Baltimore:	Thomas P. Sprunt, John E. Legge, Maurice C. Pincoffs, Henry M. Thomas, Jr.
	MASSACHUSETTS
Elmer C. Bartels, Boston:	Frank N. Allan, Lewis M. Hurxthal, William B. Breed.
Charles Sidney Burwell, Brookline:	Ernest B. Bradley, Chester M. Jones, James H. Means, William B. Breed.
Roderick Alexander Macaulay, Springfield:	Theodore S. Bacon, Laurence D. Chapin, Roger I. Lee, William B. Breed.
	MICHIGAN
Elbert Smith Parmenter, Alpena:	Robert H. Durham, Frank R. Menagh, James D. Bruce.
Charles E. Lemmon, Detroit:	Henry R. Carstens, Edward D. Spalding, James D. Bruce.
Willard D. Mayer, Detroit:	Henry R. Carstens, Frederick G. Buesser, James D. Bruce.
Lutfi Mustafa Sa'di, Detroit:	Frederick G. Buesser, Henry R. Carstens, James D. Bruce.
F. Janney Smith, Detroit:	Frank R. Menagh, Robert H. Durham, James D. Bruce.
Franklin Walter Baske, Flint:	William H. Marshall, Myrton S. Chambers, James D. Bruce.
Roy Herbert Holmes, Muskegon:	William M. LeFevre, F. Herbert Bartlett, James D. Bruce.
	MINNESOTA
Frank Joseph Heck, Rochester:	Edgar V. Allen, Porter P. Vinson, Edward L. Tuohy.
Charles Hamilton Watkins, Rochester:	Arlie R. Barnes, Edgar V. Allen, Edward L. Tuohy.
	NEW JERSEY
Ferdinand Charles Dinge, East Orange:	Joseph W. Gardam, Edward C. Klein, Jr., Clarence L. Andrews.
Paolo F. Liva, Lyndhurst:	Richard E. Knapp, Herman Trossbach, Clarence L. Andrews.
LeRoy W. Black, Rutherford:	Herman Trossbach, Richard E. Knapp, Clarence L. Andrews.
	NEW MEXICO
Carl Herman Gellenthien, Valmora:	Meldrum K. Wylder, Carl Mulky, LeRoy S. Peters.
	NEW YORK
Ferdinand Michael Jordan, Brooklyn:	James F. Weir, Mandred W. Comfort, Robert A. Cooke.
Burton L. Zohman, Brooklyn:	William S. Hubbard, Murray B. Gordon, Luther F. Warren, Robert A. Cooke.
Harold Francis Robert Brown, Buffalo:	Nelson G. Russell, Thomas J. Walsh, Allen A. Jones.
J. Frederick Painton, Buffalo:	William F. Jacobs, Carroll J. Roberts, Allen A. Jones.
Frank R. Mazzola, Jamaica:	Carl Boettiger, George Forbes, Luther F. Warren, Robert A. Cooke.

Candidates	*Sponsors*
Raeburn James Wharton, Johnson City:	Newton Thomas Saxl, Wardner D. Ayer, Robert A. Cooke.
Warren F. Kahle, Larchmont:	Arthur F. Heyl, Richard A. Kern, O. H. Perry Pepper, Robert A. Cooke.
Bernardine Thomas McMahon, Loomis:	George Foster Herben, J. Burns Amberson, Jr., Robert A. Cooke.
Joseph Hajek, New York:	Walter A. Bastedo, Samuel W. Lambert, Luther F. Warren, Robert A. Cooke.
Arthur M. Master, New York:	Emanuel Libman, Lewis A. Conner, Luther F. Warren, Robert A. Cooke.
Herman O. Mosenthal, New York:	Harlow Brooks, Carl H. Greene, Robert A. Cooke.
John James Rooney, Rochester:	James F. Rooney, John J. Finigan, Luther F. Warren, Robert A. Cooke.
Earle E. Mack, Syracuse:	Charles D. Post, I. Harris Levy, Allen A. Jones.
Stephen Horace Curtis, Troy:	Crawford R. Green, Howard F. Root, Robert A. Cooke.
	NORTH CAROLINA
Stephen Webb Davis, Charlotte:	Walter O. Nisbet, John P. Munroe, Charles H. Cocke.
Paul Allison Yoder, Winston-Salem:	Wingate M. Johnson, S. Douglas Craig, Charles H. Cocke.
	OHIO
George B. Topmoeller, Cincinnati:	Clifford J. Straehley, John E. Greiwe, A. B. Brower.
George Widmer Thorn, Columbus:	Charles A. Doan, Roy G. Pfotzer, A. B. Brower.
Raymond W. Bradshaw, Oberlin:	Lewis M. Hurxthal, Henry J. John, Roger I. Lee, A. B. Brower.
Abel Albert Applebaum, Toledo:	Louis A. Levison, John T. Murphy, A. B. Brower.
	PENNSYLVANIA
Elwood Wakefield Stitzel, Altoona:	E. Roland Snader, Jr., Augustus S. Kech, E. Bosworth McCready.
John Milnes Dyson, Hazelton:	David Riesman, Joseph C. Doane, E. J. G. Beardsley.
John M. Johnston, Pittsburgh:	Ellis M. Frost, Clement R. Jones, E. Bosworth McCready.
John Roy Spannuth, Reading:	William S. Bertolet, Alfred Stengel, O. H. Perry Pepper, E. J. G. Beardsley.
George McClintock Hutchison, Ridgway:	William G. Falconer, E. Bosworth McCready.
Ira A. Darling, Warren:	Wm. Egbert Robertson, S. Calvin Smith, E. J. G. Beardsley.
	TENNESSEE
Hugh Francis Crawford, Memphis:	Otis S. Warr, William Calvert Chaney, J. Owsley Manier.
	TEXAS
Edgar Mullins Dunstan, Dallas:	Henry M. Winans, Clarence M. Grigsby, Charles T. Stone.
Caleb Odhelius Terrell, Fort Worth:	May Owen, Will S. Horn, Charles T. Stone.
Paul Brindley, Galveston:	Boyd Reading, Titus H. Harris, Charles T. Stone.
William Lewis Marr, Jr., Galveston:	Edward H. Schwab, George Herrmann, Charles T. Stone.

Candidates	*Sponsors*
Victor Ewald Schulze, San Angelo:	Edward H. Schwab, George Herrmann, Charles T. Stone.
Paul Maiden Bassel, Temple:	George E. Brown (Deceased), Victor M. Longmire, Olin F. Gober, Charles T. Stone.
	VIRGINIA
Edward Lee Alexander, Newport News:	Walter B. Martin, C. Lydon Harrell, J. Morrison Hutcheson.
	WASHINGTON
Clyde Reynolds Jensen, Seattle:	James E. Hunter, John M. Blackford, Charles E. Watts.
	WEST VIRGINIA
George Holt Barksdale, Charleston:	Walter E. Vest, Arthur A. Shawkey, John N. Simpson.
	WISCONSIN
Vincent William Koch, Janesville:	Joseph S. Evans, William S. Middleton, Rock Sleyster.
Harold M. Coon, Stevens Point:	Joseph S. Evans, William S. Middleton, Rock Sleyster.
	CANAL ZONE
Ernst Thonnard-Neumann, Cristobal:	Lewis B. Bates, Tomás G. Guardia, William M. James.
	HAWAII
Arthur W. Duryea, Honolulu:	Harry L. Arnold, Adolph G. Schnack, James Alex. Miller.
	PUERTO RICO
Juan Antonio Pons, Floral Park, Rio Piedras:	Miguel Roses Artau, Ramon M. Suarez.
Oscar Costa-Mandry, San Juan:	Miguel Roses Artau, Ramon M. Suarez.
Rafael Rodriguez-Molina, San Juan:	Miguel Roses Artau, Ramon M. Suarez.

ELECTIONS TO ASSOCIATESHIP

March 1, 1936

Candidates	*Sponsors*
	ALABAMA
William Wallace Alexander, Florence:	Harry M. Simpson, James S. McLester, Fred W. Wilkerson.
	ARKANSAS
Lorenzo Dow Massey, Osceola:	Otis S. Warr, James B. McElroy, Oliver C. Melson.
	CONNECTICUT
Walls Willard Bunnell, Farmington:	John A. Wentworth, James E. Hutchison, Henry F. Stoll.
Frederick Erwin Tracy, Middletown:	Henry O. Colomb, George Blumer, Henry F. Stoll.
Theodore George Klumpp, New Haven:	Francis G. Blake, Willard B. Soper, Henry F. Stoll.

Candidates	*Sponsors*
MEDICAL CORPS, U. S. ARMY	
Elias Earle Cooley, Washington, D. C.:	Charles R. Reynolds.
John Dibble, Carlisle, Pa.:	Charles R. Reynolds.
George C. H. Franklin, Fort Leavenworth, Kan.:	Charles R. Reynolds.
Leon Lloyd Gardner, Washington, D. C.:	Charles R. Reynolds.
Don Longfellow, Washington, D. C.:	Charles R. Reynolds.
Alfred Mordecai, Schofield Barracks, T. H.:	Charles R. Reynolds.
Paul Adolph Schule, San Francisco, Calif.:	Charles R. Reynolds.
Seymour Crandall Schwartz, El Paso, Tex.:	Charles R. Reynolds.
Robert E. Thomas, Winthrop, Mass.:	John T. Aydelotte, George F. Aycock, Charles R. Reynolds.
Frank Wiley Wilson, Washington, D. C.:	Charles R. Reynolds.
DISTRICT OF COLUMBIA	
Isidore Lattman, Washington:	Tomás Cajigas, Arthur C. Christie, Wallace M. Yater.
Charles Hamilton Wolohon, Takoma Park, Washington:	Percy T. Magan, George T. Harding, III, William Gerry Morgan, Wallace M. Yater.
GEORGIA	
Abner Wellborn Calhoun, Atlanta:	H. Cliff Sauls, John Baker Fitts, Glenville Giddings.
ILLINOIS	
Jacob S. Golden, Chicago:	Frederick Tice, Arthur E. Mahle, James G. Carr.
William Samuel Hoffman, Chicago:	Hugh A. McGuigan, Arthur E. Mahle, James G. Carr.
Perry Julius Melnick, Decatur:	Cecil M. Jack, D. O. N. Lindberg, Samuel E. Munson.
Milton E. Rose, Decatur:	Cecil M. Jack, Otis O. Stanley, Samuel E. Munson.
Dean Field Stanley, Decatur:	Otis O. Stanley, Cecil M. Jack, Samuel E. Munson.
Harold C. Lueth, Evanston:	Nathan S. Davis, III, Andrew C. Ivy, James G. Carr.
Villairs Thomas Austin, Urbana:	Arlie R. Barnes, Harry L. Smith, Edward L. Tuohy.
INDIANA	
John Willard Ferree, Bluffton:	James G. Carr, Arthur E. Mahle, Robert M. Moore.
IOWA	
Albert Andrew Schultz, Fort Dodge:	Lee R. Woodward, Aldis A. Johnson, Tom B. Throckmorton.
KENTUCKY	
Morris M. Weiss, Louisville:	Emmet F. Horine, Morris Flexner, Chauncey W. Dowden.
MARYLAND	
James Givings Arnold, Jr., Baltimore:	Thomas P. Sprunt, Louis Krause, Maurice C. Pincoffs, Henry M. Thomas, Jr.

Candidates	*Sponsors*
Alan Bernstein, Baltimore:	Louis P. Hamburger, Sydney R. Miller, Henry M. Thomas, Jr.
Edwin Bosley Jarrett, Baltimore:	Walter A. Baetjer, Sydney R. Miller, Henry M. Thomas, Jr.
Samuel Whitehouse, Baltimore:	Thomas P. Sprunt, Charles W. Wainwright, Henry M. Thomas, Jr.
Walter LaFollette Winkenwerder, Baltimore:	Thomas P. Sprunt, George A. Harrop, Henry M. Thomas, Jr.
	MASSACHUSETTS
Richard James Clark, Boston:	Donald S. King, Chester M. Jones, James H. Means, William B. Breed.
James Addison Halsted, Dedham:	Walter Bauer, Chester M. Jones, William B. Breed.
Robert Battaile Hiden, Stockbridge:	Paul Dudley White, Chester M. Jones, James H. Means, William B. Breed.
Frank Benjamin Carr, Worcester:	George M. Albee, John J. Dumphy, Roger I. Lee, William B. Breed.
	MICHIGAN
Walter M. Bartlett, Benton Harbor:	Russell L. Cecil, Fritz B. Talbot, James D. Bruce.
Louis John Bailey, Detroit:	William J. Stapleton, Jr., John L. Chester, James D. Bruce.
Robert Berman, Detroit:	Samuel S. Altshuler, Henry R. Carstens, James D. Bruce.
Daniel P. Foster, Detroit:	Frank R. Menagh, Robert H. Durham, Charles G. Jennings (Deceased), James D. Bruce.
Nicola Gigante, Detroit:	Henry R. Carstens, Edward D. Spalding, James D. Bruce.
Ezra Lipkin, Detroit:	William H. Gordon, Hugo A. Freund, James D. Bruce.
William Lyon Lowrie, Jr., Detroit:	Frank R. Menagh, Robert H. Durham, James D. Bruce.
Clarke M. McColl, Detroit:	Frank J. Sladen, Robert H. Durham, James D. Bruce.
Solomon George Meyers, Detroit:	Henry R. Carstens, Edward D. Spalding, James D. Bruce.
Gordon B. Myers, Detroit:	Edward D. Spalding, Henry R. Carstens, James D Bruce.
Clarence E. Reyner, Detroit:	Frank R. Menagh, John G. Mateer, James D. Bruce.
Saul Rosenzweig, Detroit:	William H. Gordon, Douglas Donald, James D. Bruce.
George C. Thosteson, Detroit:	Frederick G. Buesser, Henry R. Carstens, James D. Bruce.
Russell Sherwood Anderson, Howell:	George A. Sherman, Stuart Pritchard, James D. Bruce.
	MINNESOTA
Alexander Edward Brown, Rochester:	David M. Berkman, Edward G. Bannick, Edward L. Tuohy.
John Francis Briggs, St. Paul:	Gordon R. Kamman, Edward J. Engberg, Edward L. Tuohy.
	NEW HAMPSHIRE
Charles Henry Parsons, Concord:	Henry A. Christian, Fred E. Clow, Robert B. Kerr.

Candidates	*Sponsors*
	NEW YORK
Herbert J. Ulrich, Buffalo:	Abel Levitt, William F. Jacobs, Allen A. Jones.
John Ludwig Hoffman, Kenmore:	Nelson G. Russell, Clayton W. Greene, Allen A. Jones.
N. Stanley Lincoln, Mount Morris:	Max Pinner, J. Burns Amberson, Jr., Allen A. Jones.
Herbert R. Edwards, New York:	John K. Deegan, Willard B. Soper, Luther F. Warren, Robert A. Cooke.
Oswald R. Jones, New York:	Edward P. Eglee, J. Burns Amberson, Jr., Robert A. Cooke.
Robert M. Lintz, New York:	Joseph Lintz, Willard H. Squires, Robert A. Cooke.
Charles Aden Poindexter, New York:	Irving S. Wright, A. Wilbur Duryee, Robert A. Cooke.
Aleksei A. Leonidoff, Poughkeepsie:	C. Knight Deyo, Scott Lord Smith, Luther F. Warren, Robert A. Cooke.
John N. Hayes, Saranac Lake:	Lawrason Brown, Edward P. Eglee, Allen A. Jones, Robert A. Cooke.
Ellery George Allen, Syracuse:	Edward C. Reifenstein, Maynard E. Holmes, Robert A. Cooke.
Louis Max Hickernell, Syracuse:	Maynard E. Holmes, William J. McNerney, Allen A. Jones.
J. Winthrop Pennock, Syracuse:	Maynard E. Holmes, Wardner D. Ayer, Allen A. Jones.
Jesse Randolph Pawling, Watertown:	Walter Fox Smith, William Wallace Hall, Allen A. Jones.
	NORTH CAROLINA
Kilby Pairo Turrentine, Kinston:	Paul F. Whitaker, William B. Kinlaw, Charles H. Cocke.
Arthur Thomas Wyatt, Lillington:	William T. Rainey, Paul P. McCain, Charles H. Cocke.
	OHIO
Theodore Liston Bliss, Akron:	George E. Brown (Deceased), Edward H. Rynearson, A. B. Brower.
Irving H. Schroth, Cincinnati:	Jacob L. Tuechter, David A. Tucker, Jr., A. B. Brower.
Charles Spencer Higley, Cleveland:	Charles T. Way, Joseph C. Placak, A. B. Brower.
Frank McLeod Wiseley, Findlay:	Willard C. Stoner, William H. Gordon, A. B. Brower.
	OKLAHOMA
Elmer R. Musick, Oklahoma City:	Wann Langston, John E. Heatley, Lea A. Riely.
Franklin Jesse Nelson, Tulsa:	Russell C. Pigford, C. J. Fishman, Lea A. Riely.
	PENNSYLVANIA
Joseph Warren Hundley, Jr., Philadelphia:	James E. Talley, Joseph T. Beardwood, Jr., George Morris Piersol.
Edgar Lorenz Dimmick, Scranton:	William M. Donovan, Arthur E. Davis, E. J. G. Beardsley.
	SOUTH CAROLINA
Olin Burnham Chamberlain, Charleston:	Francis B. Johnson, Joseph H. Cannon, Robert Wilson.
Gustave Patrick Richards, Charleston:	Francis B. Johnson, Kenneth M. Lynch, Robert Wilson.

Candidates	*Sponsors*
	SOUTH DAKOTA
Donald Luther Kegaries, Rapid City:	George E. Brown (Deceased), Nelson W. Barker, Julius O. Arnson.
	TEXAS
Henry Napoleon Gemoets, Houston:	Alvis E. Greer, James H. Agnew, Charles T. Stone.
	VERMONT
Ellsworth Lyman Amidon, Burlington:	Paul K. French, David A. Cooper, Clarence H. Beecher.
	WASHINGTON
Harry Joseph Friedman, Seattle:	George C. Miller, John M. Blackford, Charles E. Watts.
Treacy Henry Duerfeldt, Tacoma:	Lester J. Palmer, George C. Miller, Charles E. Watts.
	WEST VIRGINIA
Paul H. Revercomb, Charleston:	Arthur A. Shawkey, Charles A. Way, John N. Simpson.
	PUERTO RICO
Guillermo S. Marques, Arecibo:	Miguel Roses Artau, William B. Porter, Ramon M. Suarez.
Cesar Dominguez, Hamacao:	Miguel Roses Artau, William B. Porter, Ramon M. Suarez.
Manuel de la Pila Iglesias, Ponce:	Miguel Roses Artau, William B. Porter, Ramon M. Suarez.
Jose Landron, San Juan:	Miguel Roses Artau, William B. Porter, Ramon M. Suarez.
Antonio Ortiz y Ortiz, San Juan:	Miguel Roses Artau, William B. Porter, Ramon M. Suarez.
Carlos Eduardo Munoz MacCormick, Santurce:	Miguel Roses Artau, William B. Porter, Ramon M. Suarez.
	CENTRAL AMERICA
	El Salvador
Raul Arguello, Sal Salvador:	Tomás G. Guardia, Cornelius D. Briscoe, William M. James.